Evidence Report:
Diabetes and Commercial Motor Vehicle Driver Safety (Expedited Review)

Presented to

Federal Motor Carrier Safety Administration

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Prepared for

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This report is comprised of research conducted to analyze the impact of Diabetes on Commercial Motor Vehicle Driver Safety. Federal Motor Carrier Safety Administration considers evidence, expert recommendations, and other data, however, all proposed changes to current standards and guidance (guidelines) will be subject to public-notice-and-comment and regulatory processes.

Policy Statement

This report was prepared by ECRI under subcontract to MANILA Consulting Group, Inc., which holds prime Contract No. GS-10F-0177N/DTMC75-05-F-00062 with the Department of Transportation's Federal Motor Carrier Safety Administration. ECRI is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI has been designated an Evidence-based Practice Center (EPC) by the United States Agency for Healthcare Research and Quality. ECRI's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this evidence report is to provide information regarding the current state of knowledge on this topic. It is not intended as instruction for medical practice, or for making decisions regarding individual patients.

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Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the U.S. Department of Transportation, there were 137,144 non-fatal crashes involving a large truck in 2005. Of these, 59,405 were crashes that resulted in an injury to at least one individual, for a total of 89,681 injuries. In 2004,[1] 4,862 large trucks were involved in fatal accidents for a total of 5,190 fatalities. The purpose of this evidence report is to examine the relationship between diabetes mellitus and the risk for a motor vehicle crash. In order to meet the aims of this evidence report we addressed four key questions. These four key questions are as follows:

Key Question 1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?

Key Question 3: What treatment-related factors are associated with an increased incidence of severe hypoglycemia among individuals with diabetes mellitus?

Key Question 4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

The effects of the chronic complications of diabetes mellitus on driving ability were beyond the scope of the present evidence report. However, it is the intent of the program under which this report was commissioned to address these complications in later proceedings.

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by this evidence report were identified using a process consisting of a comprehensive search of the literature, examination of abstracts of identified studies in order to determine which articles would be retrieved, and the selection of the actual articles that would be included in each evidence base.

A total of seven electronic databases (Medline, PubMed (pre Medline), EMBASE, PSYCH Info, CINAHL, TRIS, the Cochrane library) were searched (through May 28, 2006). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant articles not identified by our electronic searches. Hand searches of the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria that were determined *a priori.*

[1] Fatality data for 2005 were not available at the time of writing.

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account not only the quality of the individual studies that comprise the evidence base for each key question, but also the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Analytic Methods

The set of analytic techniques used in this evidence report was extensive. Random- and fixed-effects meta-analyses were used to pool data from different studies.(1-4) Differences in the findings of studies (heterogeneity) were identified using the Q-statistic and I^2.(5-7) Sensitivity analyses, aimed at testing the robustness of our findings, included the use of cumulative fixed- and random-effects meta-analysis.(8-10) The presence of publication bias was tested for using the "trim and fill" method.(11-13)

Presentation of Findings

In presenting our findings we made a clear distinction between qualitative and quantitative conclusions and we assigned a separate "strength of evidence" rating to each of conclusion format. The strength of evidence ratings assigned to these different types of conclusion are defined in Table 1.

Table 1. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Weak	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Unacceptably Weak	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

Findings

Key Question #1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

General Answer to Key Question #1: Yes (With Qualifications)

Specific findings of our assessment of the evidence that addressed Key Question #1 are presented below:

1. **A paucity of data from studies that enrolled CMV drivers with diabetes precludes one from determining whether CMV drivers with diabetes are at increased risk for a motor vehicle accident.**

   A single, moderate quality case-control study evaluated crash risk among Canadian CMV drivers with diabetes as compared with comparable CMV drivers who did not have the disorder. While the results of this study are directly applicable to CMV drivers in the United States, it is not a high-quality study and its findings have not been replicated. Consequently, one cannot draw an evidence-based conclusion pertaining to the whether CMV drivers with diabetes are at an increased risk for a motor vehicle accident.

2. **As a group, drivers with diabetes are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Weak). The magnitude of this increased risk is small but statistically significant (Risk Ratio=1.19; 95% CI: 1.08–1.31). In other words, the crash risk for an individual with diabetes is 1.19 times greater than a comparable individual who does not have the condition (Stability of Estimate of Risk Ratio: Weak).**

   Thirteen low-moderate quality case-control studies compared crash risk among drivers with diabetes (cases) and a comparable group of drivers who do not have the disorder (controls). Quantitative analysis of outcome data from these studies found that the outcome data was homogeneous. A fixed effects meta-analysis in which these data were pooled found that the risk for crash among drivers with diabetes was 1.19 (95% CI: 1.08–1.31) times greater that the risk for crash among drivers who do not have the disorder. A series of sensitivity analyses designed to test the stability of this estimate found this estimate to be robust.

   Despite the robustness of our findings we have refrained from drawing a strong conclusion. This is because case-control studies are inherently susceptible to bias. Also, many of the studies included in the analysis were either poorly designed and/or conducted, or they were poorly reported. The most important potential source of bias to affect some of the studies in this evidence base was the failure to control for differences in exposure to risk (the amount of time driving) among the cases and controls. Having said this, the fact that data extracted from the 13 studies was homogeneous suggests that failure to control for differences in exposure did not result in biased risk-ratio estimates. Also, a sensitivity analysis in which risk-ratio data were compared between two subgroups of studies (one subgroup composed of studies that controlled for exposure and the second subgroups consisting of studies that did not) found no evidence that failure to control for exposure resulted in a systematic over-r or underestimate of the observed risk ratio.

3. **Whether drivers with type 1 or type 2 diabetes are overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.**
   Three moderate quality case-control studies, all of which enrolled individuals over the age of 65, compared the prevalence of drivers with diabetes among a cohort of drivers who had experienced a crash (cases) with the prevalence of drivers with diabetes among a cohort of drivers who had not experienced a crash (controls). Homogeneity testing found that the findings of the three included studies differed significantly. Because of the small size of the evidence base, we did not attempt to explain the inconsistency in the findings of the three studies. Consistent with the findings above, a random-effects meta-analysis found that drivers with diabetes do tend to be overrepresented among samples of drivers who have experienced a crash. However, this overrepresentation is not statistically significant (Odds Ratio=1.41; 95% CI: 0.86–2.29, P=0.1760). Consequently, we must conclude that at the present time, it remains unclear whether drivers with diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. More data are required before an evidence-based conclusion about whether drivers with diabetes are overrepresented among populations of drivers who have crashed.

4. **Whether the subgroup of drivers with diabetes that is controlled by insulin is overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.**

   All three of the case-control studies above attempted to determine whether drivers with diabetes treated using insulin are overrepresented among populations of drivers who have experienced a motor vehicle crash. These data were found to be homogeneous. Consequently, they were pooled using fixed-effects meta-analysis. As was the case in the previous analysis, the present analysis found that drivers with diabetes controlled using insulin tend to be overrepresented among samples of drivers who have experienced a crash. However, this overrepresentation is not statistically significant (Odds Ratio=1.35; 95% CI: 0.86–1.70, P=0.1695). Consequently, we conclude that at the present time, it remains unclear whether drivers with diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. More data are required before an evidence-based conclusion about whether drivers with diabetes controlled by insulin are overrepresented among populations of drivers who have crashed.

Key Question #2: Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?

General Answer to Key Question #2: Yes (With Qualifications)

The findings of our assessment of the evidence addressing Key Question 2 are presented below. None of the included studies examined the effects of hypoglycemia on simulated driving ability and cognitive or psychomotor function in a group of CMV drivers with diabetes. Also, all of the included studies examined the effects of hypoglycemia in individuals with type 1 diabetes only. No individuals with type 2 diabetes were enrolled in any included study. Even if current interstate restrictions on CMV drivers with insulin-treated diabetes are lifted, non-insulin treated individuals with type 2 diabetes will still comprise the vast majority of CMV operators who have

the disorder. Consequently, the degree to which the findings of the included studies, particularly findings related to specific driving skills, can be generalized to CMV operators is unclear.

1. **Hypoglycemia has a significant deleterious effect on the driving ability of some individuals with type 1 (or IDDM) when measured using a driving simulator (Strength of Evidence: Moderate). Due to a paucity of data (only two studies), no attempt was made to determine a quantitative estimate of the relationship between the deterioration in driving competency and blood glucose levels.**

   Three small moderate quality studies assessed the effects of induced hypoglycemia on simulated driving ability. No individuals with type 2 diabetes were enrolled in any included study. Consequently, the degree to which the findings of the included studies, particularly findings related to specific driving skills, can be generalized to CMV operators is unclear.

   All three studies found that driving ability was impaired during hypoglycemia across several variables. Despite agreement across studies that driving ability is impaired by hypoglycemia, there is little agreement as to exactly which aspects of driving ability are most vulnerable to hypoglycemia and at what levels of hypoglycemia these impairments begin to become manifest.

2. **Hypoglycemia has a significant deleterious effect on the cognitive and psychomotor function of individuals with type 1 (or IDDM) as measured by a number of different tests of cognitive function (Strength of Evidence: Moderate). Due to the fact that no more than two studies used the same tests of cognitive or psychomotor function, no attempt was made to determine a quantitative estimate of the relationship between functional loss and blood glucose levels.**

   Ten small low-to-moderate quality studies assessed the effects of induced hypoglycemia on cognitive and psychomotor function. These 10 studies consistently demonstrated that moderate hypoglycemia (blood glucose levels in the region of 2.5-3.0 mmol/L[45–54 mg/dl]) had an acute deleterious effect on the ability of some (but not all) individuals with insulin-dependent diabetes to perform a wide variety of cognitive and psychomotor tasks. At the present time no comparable data sets are available for individuals who do not require insulin to control their diabetes.

Key Question #3: What treatment-specific risk factors are associated with an increased incidence of severe hypoglycemia among individuals with diabetes mellitus?

General Answer to Key Question #3: Unclear

Known treatment-related risk factors for an increased incidence of severe hypoglycemia include lower HbA1c, the use of insulin, and intensified insulin treatment (multiple injections per day). The aim of this question was to determine the effect of specific treatment options (different types of insulin, different types of oral hypoglycemic agents, different treatment combinations) on the incidence of severe hypoglycemia among individuals with diabetes.

The most appropriate study designs for the evaluation of risk factors associated with a particular condition among representative populations while controlling for other known risk factors come from epidemiology. Consequently, our searches focused on identifying epidemiological studies

(case-control studies or cohort studies) that attempted to determine the relative risk for hypoglycemia that is associated with different treatment options, different treatment regimes, or different modes of treatment administration.

Most available information on the frequency of the occurrence of hypoglycemia among patients who undergo treatment for diabetes comes from efficacy and safety studies (usually randomized controlled trials). Although randomized controlled trials (RCTs) are often considered, "the gold standard cohort study," when used to assess treatment efficacy and safety of a treatment, RCTs have a number of shortcomings, including the following:

- Safety and effectiveness trials tend to enroll carefully screened and selected patients who are not representative of the broader population.
- Safety and efficacy trials use protocols that are not reflective of disease management in the broader population.
- Safety and effectiveness trials tend to be small and short-term, which precludes an accurate determination of the true incidence of hypoglycemia.

In order to ensure that any assessment of the available evidence addressing Key Question 3 was meaningful we developed restrictive retrieval and inclusion criteria that were designed to exclude studies that suffer from the shortcomings described above. As a consequence, several thousand articles were screened but not retrieved because they were either not generalizable to the broader population, they utilized protocols that were not reflective of how treatment would be used in clinical practice, or they were small or used a short follow up time that precluded accurate estimation of the incidence of hypoglycemia.

Key Question #4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

General Answer to Key Question #4: Unclear

The findings of our analysis of the best available evidence pertaining to the effectiveness of BGAT are presented below:

1. **BGAT improves the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels (Strength of Evidence: Moderate)**

   Qualitative assessment of the data from five moderate quality studies consistently demonstrated that BGAT improves the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels.

2. **A paucity of consistent evidence precludes a determination from being made concerning whether BGAT is effective in reducing the incidence of severe hypoglycemia.**

   Simply because individuals who have undergone BGAT demonstrate improvements in their ability to accurately estimate their blood glucose levels does not necessarily mean that BGAT will lead to a reduction in the incidence of severe hypoglycemia. Consequently, we looked for direct evidence of a negative relationship between BGAT and the incidence of severe hypoglycemia. Two moderate-quality studies that enrolled individuals with type 1 diabetes presented data on the incidence of severe hypoglycemia

following exposure to BGAT. The results of these two small studies were inconsistent, with one study finding a benefit while the other study did not. The inconsistencies in the findings of the two studies cannot be explained. Given this, it remains unclear whether exposure to BGAT results in measurable reductions in the incidence of severe hypoglycemia among individuals with type 1 diabetes.

Conclusions

On the Findings of the Evidence Report

Direct evidence pertaining to diabetes and CMV driver safety was extremely scarce; only one such study (which addressed Key Question #1) was included in this evidence report. Consequently, we were obliged to turn to evidence from studies that assessed the relationship between diabetes and driver safety in the general population. On average, drivers in the general population differ from CMV drivers in that they are far less experienced. On the other hand, CMV drivers are exposed to far more risk than the average driver by virtue of the fact that they are driving for longer periods of time over far greater distances in a large variety of traffic environments. Whether superior driving experience outweighs the risks associated with increased driving exposure is unclear; however, the fact that truck driving is considered to be a very dangerous occupation suggests that it does not.

Our assessment of the available evidence pertaining to crash risk found that the average driver with diabetes (type 1 or type 2) has a small but significant incremental increase in the risk for motor vehicle crash over and above that of a comparable individual who does not have the disorder (Risk Ratio=1.19, 95% CI; 1.08–1.31). In other words, the risk of an individual with diabetes being involved in a motor vehicle crash is approximately 1.19 times greater than that of a comparable individual who does not have the disorder.

One possible cause of the excess risk for a crash seen in individuals with diabetes is incapacitation due to hypoglycemia. Indeed there is ample anecdotal evidence in the literature (in the form of case reports) to suggest that some crashes experienced by individuals with diabetes can be attributed to hypoglycemia. To date no well designed study has provided direct evidence supporting the contention that hypoglycemia is the major contributor to the increased risk for crash among individuals with diabetes. Indirect evidence, however, is reasonably plentiful. Our analysis of data from 13 independent studies consistently found that moderate-to-severe hypoglycemia has a deleterious effect on the driving ability, cognitive function, and psychomotor function of some individuals with type 1 diabetes. Due to a paucity of acceptable data, we were unable to determine the extent to which hypoglycemia affected these measures in individuals with type 2 diabetes.

Because there is a reasonably large body of literature showing that hypoglycemia occurs more often among individuals treated with insulin than among those treated by pharmacotherapy or diet alone, one would might reasonably expect that insulin-treated drivers are at a higher risk for a motor vehicle crash risk than non-insulin treated drivers. Surprisingly, a series of analyses designed to determine the excess risk associated with insulin treatment did not confirm this. One possible explanation for the finding that drivers with insulin-treated diabetes do not appear to be at a higher risk for a motor vehicle crash than drivers with non-insulin treated diabetes is that a process of self-selection occurs among individuals with insulin-treated diabetes whereby the most severely affected individuals either restrict their driving or do not drive at all. As a

consequence, crash risk estimates determined for drivers with insulin-treated diabetes are based on a subset of individuals with lower rates of hypoglycemia than would be seen if all individuals with insulin-treated diabetes drove.

Because there is evidence (albeit indirect) to suggest that hypoglycemia is a primary contributor to the excess crash risk observed among individuals with diabetes, a number of groups have attempted to develop programs that aim to diminish its incidence. One such program is BGAT (Blood Glucose Awareness Training). BGAT is a psychoeducational intervention program designed to assist individuals with type 1 diabetes in managing and maintaining tight diabetic control. The value of BGAT in managing and maintaining control in individuals with type 2 diabetes has not been assessed. Our analysis of studies of the effectiveness of BGAT found that the program was effective in improving the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels. However, currently available evidence has not consistently demonstrated that this improvement in blood glucose level estimation leads to measurable reductions in the incidence of severe hypoglycemia among individuals with type 1 diabetes.

On the Limitations of this Evidence Report

The findings of this evidence report cannot be viewed as definitive. Like all systematic reviews the soundness of the answers it provides is entirely dependent on the quality, quantity, consistency, robustness, and generalizability (to the specific target population of interest) of the available evidence. In this report, the best available evidence was of low-to-moderate methodologic quality. Also, because only one study was directly generalizable to CMV drivers, the generalizability of the findings of this evidence report to this specific population is unclear.

On the Need for Further Studies

The lack of data from CMV drivers is, to some degree, a consequence of the fact that individuals with insulin-treated diabetes have until recently been unable to obtain an interstate CMV drivers license. However, several States' allow individuals to drive large trucks within State and individuals with non-insulin treated diabetes are not precluded from obtaining an interstate CMV drivers license. Consequently, populations of CMV drivers with diabetes do exist and crash risk studies need to be performed in these populations so that the risk of crash among CMV drivers can be determined more definitively.

The fact that non-insulin treated diabetes does not exclude an individual from obtaining a CMV license, the fact that individuals with non-insulin treated diabetes is common, and the fact that studies on motor vehicle crash risk associated with this type of diabetes are rare, suggests that there is a general belief that non-insulin dependent diabetes is not a serious threat to road traffic safety. This belief is supported to some degree by the fact that the incidence of severe hypoglycemia is lower among individuals with non-insulin dependent diabetes. The findings of this evidence report, however, suggest that this belief may be misplaced. Our analyses of the available data suggest that the excess crash risk associated with insulin and non-insulin dependant diabetes is similar. Consequently, there is an urgent need for direct comparisons of crash risk data from reasonably well matched individuals with non-insulin and insulin dependent diabetes to be performed.

Preface

Organization of Report

This evidence report contains five major sections: 1) *Background*, 2) *Current U.S. Federal Regulatory and Medical Advisory Criteria*, 3) *Methods*, 4) *Synthesis of Results*, and 5) *Conclusions*. These major sections are supplemented by extensive use of appendices.

In the *Background* section, we provide background information about diabetes, including details about its epidemiology, diagnosis, treatment, and its potential impact on driver safety. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature searching, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesis of clinical study results. The *Synthesis of Results* section of this report is organized by Key Question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize available data extracted from included studies either qualitatively or, when the data permit, qualitatively and quantitatively (using meta-analysis). Each section in the *Synthesis of Results* section closes with our conclusions that are based on our assessment of the available evidence. This evidence report ends with a *Conclusions* section that briefly summarizes the answers to each of the questions addressed in it.

Scope

Workers in the trucking industry experienced the most fatalities of all occupations, accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truckers were involved in highway crashes. According to statistics from the U.S. Department of Transportation, there were 137,144 crashes involving a large truck in 2005. Of these, 59,405 were crashes that resulted in an injury to at least one individual, for a total of 89,681 injuries. In 2004,[2] 4,862 large trucks were involved in fatal accidents, for a total of 5,190 fatalities. This report aims to examine the relationship between diabetes mellitus and the risk for a motor vehicle crash. In order to meet the aims of this evidence report we address four key questions. These four key questions are as follows:

> *Key Question 1:* Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?
>
> *Key Question 2:* Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?
>
> *In addressing this question we examine the relationship between hypoglycemia and the following direct and indirect outcome measures:*
>
> *a) Simulated driving performance (indirect)*
>
> *b) Driving-related cognitive and psychomotor performance (indirect)*

[2] Fatality data for 2005 was not available at the time of writing.

Key Question 3: What treatment-related factors are associated with an increased incidence of severe hypoglycemia among individuals with diabetes mellitus?

Potential factors to be assessed in addressing this question include the following:

a) *Mechanism of glycemic control (insulin, 1st generation[3] sulfonylureas, 2nd generation[4] sulfonylureas, meglitinides, and other hypoglycemic drugs used to control blood glucose levels)*

b) *Route of insulin administration (inhaled, subcutaneous injection, pump)*

Key Question 4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

The effects of the chronic complications of diabetes mellitus on driving ability are beyond the scope of the present evidence report. However, these complications will be discussed in later proceedings.

[3] 1st generation sulfonylureas include: tolbutamide, acetohexamide, tolazamide, chloropropamide.

[4] 2nd generation sulfonylureas include: glipizide, glyburide, glimepiride

Background

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate (http://www.bls.gov/iif/oshcfoiarchive.htm#2004charts), accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the U.S. Department of Transportation (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2005), there were 137,144 non-fatal crashes involving a large truck in 2005. Of these, 59,405 were crashes that resulted in an injury to at least one individual, for a total of 89,681 injuries. In 2004,[5] 4,862 large trucks were involved in fatal accidents for a total of 5,190 fatalities (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2004). The purpose of this evidence report is to assess and summarize the available data pertaining to the relationship between diabetes mellitus and motor vehicle crash risk.

Diabetes Mellitus

Diabetes mellitus is a group of diseases characterized by abnormally high levels of blood glucose. These high blood glucose levels result from defects in insulin secretion, insulin action, or both. Diabetes mellitus is typically classified as type 1 or type 2 diabetes. Another less common form of diabetes is gestational diabetes; a form of diabetes that occurs in some women during pregnancy.

Type 1 diabetes was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. Type 1 diabetes may account for 5 to 10 percent of all diagnosed cases of diabetes. Risk factors are less well defined for type 1 diabetes than for type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes.(14)

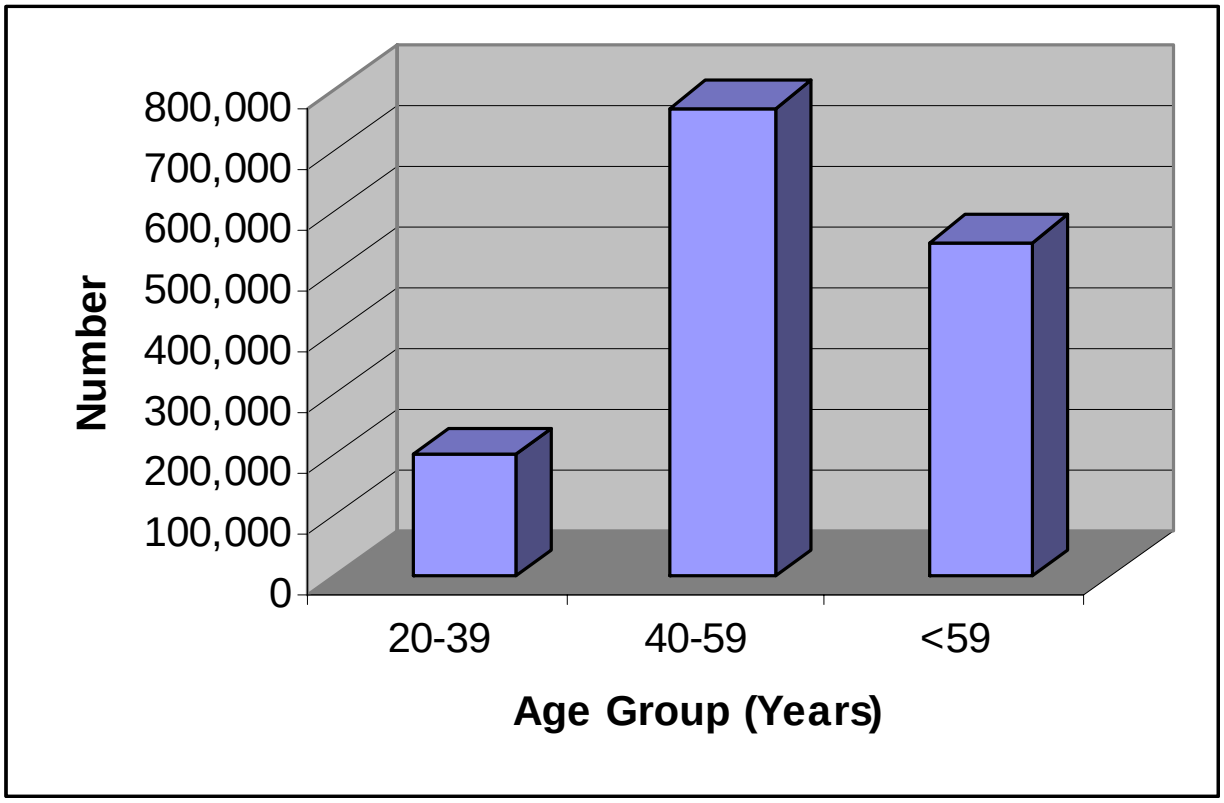
Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes may account for about 90 to 95 percent of all diagnosed cases of diabetes. Risk factors for type 2 diabetes include older age, obesity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at particularly high risk for type 2 diabetes.(14)

Prevalence and Incidence of Diabetes Mellitus

According to the most recent statistics from the National Institute of Diabetes and Digestive and Kidney Diseases, an estimated 20.8 million people have diabetes in the United States. Of these, 14.6 million have been diagnosed and an estimated 6.2 million remain undiagnosed.(15) The incidence of new cases of diabetes among individuals aged 20 years or older in the United States was estimated to be 1.5 million in 2005.(15) Figure 1 displays the number of new cases of diagnosed diabetes among U.S. adults aged 20 years or older. In the year 2005, there were about 202,000 new cases among people aged 20–39 years; 727,000 new cases among people aged 40–59 years; and 575,000 among people aged 60 years and older.

[5] Fatality data for 2005 was not available at the time of writing.

Figure 1. Estimated Incidence of Diabetes in 2005 (≥20 years, by age group—United States)(15)



Economic Burden of Diabetes

The economic burden of diabetes on the U.S. economy is significant. According to a study commissioned by the American Diabetes Association and performed by the Lewin Group, the direct and indirect expenditures attributable to diabetes in 2002 were approximately $132 billion. Estimates of direct medical expenditures totaled $91.8 billion and comprised $23.2 billion for diabetes care, $24.6 billion for chronic complications attributable to diabetes, and $44.1 billion for excess prevalence of general medical conditions.(16) Attributable indirect expenditures resulting from lost workdays, restricted activity days, mortality, and permanent disability due to diabetes totaled $39.8 billion. U.S. health expenditures for the health care components included in the study totaled $865 billion, of which $160 billion was incurred by people with diabetes. Per capita medical expenditures totaled $13,243 for people with diabetes and $2,560 for people without diabetes. When adjusting for differences in age, sex, and race/ethnicity between the population with and without diabetes, people with diabetes had medical expenditures that were approximately 2.4 times higher than expenditures that would be incurred by the same group in the absence of diabetes.

Treatment of Diabetes Mellitus

Treatments for diabetes mellitus aim to maintain blood glucose levels near normal (euglycemia) at all times. Because type 1 and type 2 diabetes have different etiologies, the treatments for these disorders differ. A lack of insulin production by the pancreas makes type 1 diabetes particularly difficult to control. Treatment requires a strict regimen that typically includes a carefully calculated diet, planned physical activity, home blood glucose testing several times a day, and multiple daily insulin injections. Treatment for type 2 diabetes typically includes diet control, exercise, home blood glucose testing, and, in some cases, oral medication and/or insulin. Approximately 40 percent of people with type 2 diabetes require insulin injections.

As stated above, currently available treatment options for individuals with diabetes include insulin (required by all individuals with type 1 diabetes and up to 40% of those with type 2 diabetes) and a number of different classes of oral agents. Table 2 provides a list of oral agents and insulin preparations that are currently used by individuals with diabetes in the United States. Included in the table are links to World Wide Web sites (primarily manufacturer's sites) where the reader can obtain labeling information. Accurate and publicly available product labeling information is required by FDA in order for any drug to be marketed in the United States. Product labeling provides details on the active agent, its dosing regimen, its indications and contraindications, and provides details of adverse events that have occurred (or may occur) among individuals using the medication.

Table 2. Treatments for Diabetes Currently Available in the United States

Class	Generic	Trade Names	Diabetes Type	Link to labeling information*	Comments
Oral Agents					
Sulfonylureas–1st generation	Acetohexamide	Dymelor®	2	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682478.html	
	Chlorpropamide	Diabinese®	2	www.pfizer.com/download/uspi_diabinese.pdf	
	Tolazamide	Tolinase®	2	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682482.html	
	Tolbutamide	Orinase®	2	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682481.html	
Sulfonylureas–2nd generation	Glimepiride	Amaryl®	2	www.fda.gov/cder/foi/label/2005/020496s015lbl.pdf	
	Glipizide	Glucotrol® Glucotrol® XL	2	www.pfizer.com/pfizer/download/uspi_glucotrol.pdf	
	Glyburide	DiaBeta® Glynase® Micronase®	2	www.pfizer.com/pfizer/download/uspi_glynase.pdf	
Biguanides	Metformin	Glucophage®	2	www.fda.gov/cder/foi/label/2000/21202lbl.pdf	When used as monotherapy, metformin does not cause hypoglycemia and is thus termed an "antihyperglycemic" agent and not a hypoglycemic agent
Alpha-Glucosidase Inhibitors	Acarbose	Precose®	2	http://www.glucobay.com/en/professional/facts/index.html?m=1	Does not cause hypoglycemia by itself
	Miglitol	Glyset®	2	http://www.glyset.com/	Does not cause hypoglycemia by itself

Class	Generic	Trade Names	Diabetes Type	Link to labeling information*	Comments
Thiazolidinediones	Pioglitazone	Actos®	2	http://www.actos.com/	
	Rosiglitazone	Avandia®	2	http://www.avandia.com/	
	Troglitazone	Withdrawn from market due to increased incidence of drug-induced hepatitis			
Meglitinides	Repaglinide	Prandin®	2	http://www.prandin.com/	
	Nateglinide	Starlix®	2	http://www.starlix.com/	
Glucagon-like peptide-1 (GLP-1) agonist	Exenatide	Byetta®	2	http://www.byetta.com/index.jsp	Does not cause hypoglycemia by itself
Injected Agents					
Insulin	Porcine or Beef insulin	Manufacturing of beef insulin for human use in the United States discontinued in 1998. From January 2006, pork insulin for human no longer manufactured or marketed in the United States			
	Aspart	NovoLog®	1 or 2	http://www.novolog.com/	
	Insulin Glargine	Lantus®	1 or 2	http://www.lantus.com/	
	Lente	No longer available in the United States.			
	Lispro	Humalog®	1 or 2	http://www.lillydiabetes.com/product/humalog.jsp?reqNavId=5.1	
	NPH	Humulin® N Novolin® N ReliOn® (Wal-Mart)	1 or 2	http://www.lillydiabetes.com/product/humulin_family.jsp?reqNavId=5.3 http://www.walmart.com/catalog/product.do?product_id=2139093	
	Premixed	NovoLog® Mix 70/30 Humalog® 75/25 Humulin® 70/30 Humulin® 50/50	1 or 2	http://www.novologmix70-30.com/ http://www.lillydiabetes.com/product/humalog_mix_75_25.jsp?reqNavId=5.2 http://www.lillydiabetes.com/product/humulin_family.jsp?reqNavId=5.3	
	Regular	Humulin® R Novolin® R	1 or 2	http://www.lillydiabetes.com/product/humulin_family.jsp?reqNavId=5.3 www.fda.gov/medwaTCH/SAFETY/2005/Oct_PI/Novalin%20R_PI.pdf	
	Ultralente	No longer available in the United States.			
Inhaled Agents					
Insulin	Insulin human (rDNA origin) inhalation powder	Exubra	1 or 2	http://www.exubera.com/	

*If you are viewing this table using Microsoft Word the links are active.

Sulfonylureas

This was the first class of oral drugs available for the treatment of type 2 diabetes. Introduced in 1955, the sulfonylureas were the only blood sugar-lowering medications available in the United States until 1995. Sulfonylureas can be further classified into two groups or generations, based on their potency, duration of action, and drug interactions/side effects profiles. Regardless of generation, all sulfonylureas work in the same way to lower blood sugar; they stimulate beta-cells in the pancreas to produce more insulin.

First-generation sulfonylureas are not used as extensively today as the newer second-generation sulfonylureas because the newer drugs have demonstrated better side-effect profiles. First-generation sulfonylureas include acetohexamide, chlorpropamide, tolazamide, and tolbutamide.

Second-generation sulfonylureas include glimepiride, glipizide, Glipizide ER, and glyburide. These latter drugs are all similarly effective in lowering blood sugar levels. However, some minor differences do exist among the second-generation sulfonylureas. Glipizide produces a more rapid lowering of blood sugar compared with glyburide. Glyburide, on the other hand, is more potent than glipizide. Glimepiride and glipizide ER are longer acting than the other two sulfonylureas.

Biguanides

Biguanides are used to treat type 2 diabetes. They work by decreasing the absorption of glucose by the intestines, decreasing the production of glucose in the liver, and by increasing the body's ability to use insulin more effectively. Metformin is currently the only drug in this category. When used as monotherapy, metformin does not cause hypoglycemia; thus metformin is classified as an antihyperglycemic agent rather than a hypoglycemic agent.

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (AGIs) are given with meals and work by slowing the breakdown of the complex sugars into glucose. This results in delayed glucose absorption and lower blood sugars following meals. The AGIs may be used alone or in combination with other medications for diabetes. Glyset and Precose are the only available AGIs. Glyset is only indicated for combination therapy with a sulfonylurea, while Precose may be used with a sulfonylurea, metformin, or insulin. When used alone AGIs do not cause hypoglycemia.

Thiazolidinediones

The thiazolidinediones are a relatively new group of drugs with a mechanism of action that differentiates them from most hypoglycemic agents. Unlike biguanides and sulfonylureas, thiazolidinediones decrease hepatic fat content and increase insulin sensitivity in muscle. These properties would seem to make the drugs particularly useful in patients with insulin-resistant type 2 diabetes, but no data are currently available to help identify the patients who would respond best to these drugs. Rosiglitazone and pioglitazone are currently approved in most countries for the treatment of hyperglycemia in patients with type 2 diabetes, either as monotherapy or in combination with sulfonylureas or metformin. In the United States, both drugs have also been approved for use in combination with insulin, provided certain precautions are followed. The thiazolidinedione medication troglitazone (Rezulin) has been removed from the market in the United States and some European countries. Troglitazone has been shown to cause severe liver problems in a small number of people who take it. When used alone, thiazolidinediones do not cause hypoglycemia.

Meglitinides

Meglitinides are non-sulfonylurea insulin secretagogues that lower blood sugar levels by increasing the release of insulin from the pancreas. The drugs in this class are unique because they are relatively short acting compared with other classes of drugs used to treat type 2 diabetes. The meglitinides may be used alone or in combination with metformin. Two meglitinides are approved for marketing in the United States; Prandin, derived from benzoic acid and approved by the FDA in 1997, and Starlix, derived from D-phenylalanine and approved in 2000.

Insulin

Insulin is produced by the beta cells in the islets of Langerhans in the pancreas. When glucose enters the blood, the pancreas should automatically produce the right amount of insulin to transport glucose into cells. Individuals with type 1 diabetes produce no insulin. Individuals with type 2 diabetes do not always produce enough insulin or they develop a resistance to the hormone that diminishes the uptake of glucose into target cells. There are currently more than 20 types of insulin products available in the United States; each form has a different time of onset and duration of action (see: http://www.fda.gov/fdac/features/2002/chrt_insulin.html).

Until this year, all currently available insulin delivery devices injected insulin through the skin and into the fatty tissue below. Most individuals inject insulin with a syringe while a smaller number of individuals use insulin pens, jet injectors, or insulin pumps. This year Pfizer will be introducing an inhaled form of insulin onto the U.S. market. In addition, several other new approaches (e.g., insulin patches) for taking insulin are under development, but these remain experimental and have not yet been approved for marketing in the United States.

Diabetes and Driver Safety

A number of acute and chronic complications associated with diabetes may affect driving competency. Chronic complications associated with diabetes mellitus that may compromise driver safety include cardiovascular disease, diabetic neuropathy, and diabetic retinopathy. The effects of the chronic complications of diabetes mellitus on driving ability will be discussed in later proceedings.

The most important acute threat to driver safety among individuals with diabetes mellitus is generally considered to be hypoglycemia. Hypoglycemia is a clinical syndrome that results from abnormally low levels of blood glucose. The symptoms of hypoglycemia can vary from person to person, as can their severity. In general, however, the body's biochemical response to hypoglycemia usually start when blood sugar levels fall below 65 to 70 mg/dl (3.6 to 3.9 mmol/L). Below this point, the body responds by increasing the secretion of counter-regulatory hormones. If the blood glucose level falls below 60 mg/dl (3.3 mmol/L), physical symptoms begin to become apparent–the onset of sweating, tremor, hunger, a feeling of anxiety, and palpitations. These symptoms, when recognized, act as a warning signal to individuals with diabetes that they should take immediate steps to increase their blood glucose levels. If these warning signs are ignored (or go unrecognized–hypoglycemic unawareness) blood glucose levels may continue to fall. When blood glucose levels fall below 50 mg/dl (2.8 mmol/L) the central nervous system begins to be starved of glucose and symptoms of neuroglycopenia (weakness, lethargy, blurred vision, dizziness, trouble speaking) and cognitive dysfunction begin to occur. Further reductions in blood glucose levels may result in seizures, coma, and death.

Incidence of Severe Hypoglycemia

Several studies have investigated the incidence of severe hypoglycemia[6] among individuals with diabetes mellitus. Relevant data from these studies are summarized in Table 3. As can be seen, estimates of the incidence of severe hypoglycemia vary considerably across studies. This variation in incidence rates is likely the consequence of several factors: differences in the population mix, slight differences in the definition of severe hypoglycemia, and differences in

[6] We define a severe hypoglycemic event as one that is severe enough for the affected individual to require the assistance of a third party.

the treatment regime used. A number of general observations pertaining to the differences in the reported incidence of severe hypoglycemia are listed below.

1. The incidence of severe hypoglycemia appears to be higher among individuals with type 1 diabetes than with type 2 diabetes that require insulin to control their diabetes.(17,18) Heller et al.(17) found that proportionally more individuals with type 1 diabetes than individuals with type 2 diabetes experienced at least one episode of clinically significant hypoglycemia (defined as a interstitial glucose level of less than 2.2 mmol/l for greater than 20 minutes) over a .(19,20) Donnely et al.(18) noted that the incidence of severe hypoglycemia among a cohort of individuals with type 1 diabetes was 3.29 times greater than that seen among individuals with type 2 diabetes. MacLeod et al.(19) and Casparie & Elving(20) reported similar findings, although the incidence ratios observed by these two groups were slightly smaller (2.33 and 2.40 respectively).
2. The incidence of severe hypoglycemia among individuals with type 1 diabetes, but not insulin treated type II diabetes, appears to be higher than that observed among individuals with type 2 diabetes treated with oral hypoglycemics alone. Shorr et al.(21) found that the incidence of severe hypoglycemia among a cohort of elderly individuals with insulin treated diabetes (type 1 and type 2), was 1.6 times greater than that observed among individuals whose diabetes was controlled using a sulfonylurea. Recent data from Heller et al.(17) suggests that this difference is not observed when one compares individuals with insulin treated type 2 diabetes. These latter investigators found no evidence of a difference in the proportion of individuals who experienced at least one episode of severe hypoglycemia among three groups of individuals with type 2 diabetes; individuals controlled with sulfonylureas alone, individuals controlled with insulin for <2 years, and individuals controlled with insulin for >5 years.
3. The incidence of severe hypoglycemia among individuals with type 2 diabetes appears to be higher among individuals treated with a combination of insulin and a sulfonylurea than that observed among individuals treated with either drug alone. Shorr et al.(21) found that the incidence of severe hypoglycemia among individuals with type 2 diabetes treated with a combination of insulin and a sulfonylurea was 1.2 times greater than that observed among those controlled with insulin alone and two times greater that that observed among those controlled using a sulfonylurea.
4. The tighter the control of blood sugar levels, the higher the incidence of severe hypoglycemia appears to be. The Diabetes Control and Complications Trial (DCCT)(22) found that the incidence of severe hypoglycemia was 3.26 higher among individuals with type 1 diabetes who underwent intensive insulin therapy (either by multiple daily injections or via an insulin infusion pump) than among comparable individuals who used a less intensive insulin-therapy protocol (one or two injections per day). It should be noted, however, that these data are based on treatment regimes that are now dated. Thus, it is possible that the advent of newer insulin analogs will allow tight glycemic control to be attained while reducing the risk for severe hypoglycemia. Indeed there is evidence in the literature to support this latter contention.(23-28)(see also Table J-1 of Appendix J) The reader should note however that no study to date has demonstrated that the excess risk associated with maintaining tight glycemic control among individuals with type 1 diabetes can be eliminated.

5. The incidence of severe hypoglycemia among individuals with type 1 diabetes and impaired kidney disease is higher than that observed among individuals with normal kidney function who are otherwise comparable. Mulhauser et al.(29) reported that the incidence of severe hypoglycemia among individuals with type 1 diabetes and reduced kidney function was more than five times greater than that seen in similar individuals with normal kidney function.

Table 3. Reported Hypoglycemia Incidence Rates

Reference	Year	N=	Diabetes type (special population)	Severe hypoglycemic events/patient–year
Heller et al.(17)	2006	400	Type 1 <5 years duration (n=50) Type 1 >15 years duration (n=57) Type 2 tablets (n=108) Type 2 insulin <2 years (n = 89) Type 2 insulin >5 years (n = 77) Non-diabetic controls (n = 19)	0.46 (0.33 to 0.60)* 0.61 (0.61 to 0.73)* 0.22 (0.15 to 0.31)* 0.20 (0.13 to 0.30)* 0.22 (0.14 to 0.33)* 0.32 (0.15 to 0.54)*
Donnely et al.(18)	2004	267	Type 1 (n=94) Type 2 † (n=173)	Type 1: 1.15 Type 2†: 0.35
Pederson-Bjergaard et al.(30)	2004	1076	Type 1	1.30
Johnson et al.(31)	2002	1113	Type 1 and Type 2	0.05
Ter Braak et al.(32)	2000	195	Type 1	1.50
Muhlhauser et al.(33)	1998	684	Type 1	0.19
Bott et al.(34)	1997	636	Type 1	0.17
Gold et al.(35)	1997	60	Type 1	1.6
Shorr et al.(21)	1997	19,932	Type I and Type 2 (≥65 years old-Medicaid population)	All: 0.018 Insulin only: 0.028 Sulfonylureas only: 0.017 Insulin and sulfonylureas: 0.034
Pampanelli et al.(36)	1996	112	Type 1	0.01
DCCT(22)	1995	1441	All Type 1 IIT (n=711) CIT (n=730)	Overall: NR IIT: 0.62 CIT: 0.19
Bell et al.(37)	1994	211	Type 1	0.35
MacLeod et al.(19)	1993	600	Type 1 (n=544) Type 2† (n=54)	Type 1: 1.70 Type 2†: 0.73
Mulhauser et al.(29)	1991	90	All Type 1 Impaired kidney function: (n=44) Normal kidney function (n=46)	Overall: NR Impaired kidney function: 1.28 Normal kidney function: 0.25
Pramming et al.(38)	1990	411	Type 1	1.51
Nilsson et al.(39)	1988	≈900*	Insulin dependent	0.07
Casparie & Elving(20)	1985	400	All insulin dependent Type 1 (n=200) Type 2 (n=200)	Overall: 0.08 Type 1: 0.12 Type 2: 0.05

CIT=Conventional Insulin Therapy; IIT=Intensive Insulin Therapy; *Proportion experiencing at least one episode where interstitial glucose levels fell below 2.2 mmol/l for more than 20 minutes; †insulin dependent Type 2

The Occurrence of Hypoglycemia While Driving

A number of studies have attempted to determine the proportion of individuals with diabetes who have experienced a hypoglycemic event while driving. The findings from these studies are summarized in Table 4. These data show that experiencing a hypoglycemic episode while driving is not a rare event and that a significant proportion of individuals attribute a crash that they were involved in to hypoglycemia.

Table 4. Occurrence of Hypoglycemia While Driving

Reference	Year	N=	Diabetes type (special population)	% drivers experiencing ≥1 hypoglycemic episode while driving	% drivers experiencing ≥1 crash attributed to hypoglycemia
Cox et al.(40)	2003	673	Type 1 (n=341)	22% in previous 6 months 17% experienced a severe hypoglycemic event while driving in previous 2 years	NR
			Type 2 (n=332)	4% in previous 6 months 5% experienced a severe hypoglycemic event while driving in previous 2 years	NR
MacLeod et al.(19)	1993	600	Type 1 (n=544) Type 2* (n=54)	NR	2.9% in previous year
Ward et al.(41)	1990	158	Type 1 diabetes	40% during driving life	13% during driving life
Stevens et al.(42)	1989	354	Type 1 diabetes	18.4% in previous year	12% during driving life
Eadington et al.(43)	1988	187	Type 1 diabetes	NR	3.7% during previous 8 years
Songer et al.(44)	1988	127	Insulin dependent	NR	5.2% during driving life
Clarke et al.(45)	1980	157	Type 1 diabetes	40.4% during driving life	NR
Frier et al.(46)	1980	250	Insulin dependent	34.4% over driving life	5.0% during driving life %

*All individuals with type 2 diabetes insulin-treated

Hypoglycemic Unawareness

Hypoglycemic unawareness is the reduced ability or failure to recognize hypoglycemia at the physiological plasma glucose concentration at which warning symptoms normally occur. Patients with hypoglycemia unawareness either do not realize that the plasma glucose is decreasing, or they ultimately feel the symptoms, but at much lower plasma glucose levels than normal. Such individuals are more prone to incapacitation consequent to hypoglycemia because preventative action that will increase blood glucose levels is not taken in a timely manner. In an individual with normal hypoglycemic awareness the first response to a drop in plasma glucose level below 70 to 65 mg/dl is the acute release of counter-regulatory hormones (glucagon and epinephrine). In some individuals with type 1 diabetic subjects, the protective glucagon response to hypoglycemia begins to fail within two years of the onset of the disease. The prevalence of hypoglycemia unawareness becomes more common among individuals with type 1 diabetes as the duration of the disease increases.(47) The etiology underlying the development of hypoglycemic unawareness is not known.

Federal Regulatory and Medical Advisory Criteria for CMV Operators

Current Federal Regulatory Criteria for CMV Operators

Federal Motor Carrier Safety Regulations (FMCSRs), found in 49 Code of Federal Regulations (CFR) 301 through 399, cover businesses that operate CMVs in interstate commerce. FMCSRs that pertain to fitness to drive a commercial vehicle are found in 49 CFR 391 Subpart E. Only motor carriers engaged purely in intrastate commerce are not directly subject to these regulations. However, intrastate motor carriers are subject to State regulations, which must be identical to, or compatible with, the Federal regulations in order for States to receive motor carrier safety grants from FMCSA. States have the option of exempting CMVs with a gross vehicle weight rating of less than 26,001 lbs.

The following subsection contains the federal regulatory and medical advisory standards found in the FMCSRs (49 C.F.R. section 391.41) that specifically apply to drivers with diabetes mellitus. Complete FMCSRs can be found at the Web site: http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrguide.asp?section_type=A.

Subpart E: Physical Qualifications and Examinations

§391.41 Physical qualifications for drivers (relevant to individuals with diabetes)

(a) A person shall not drive a commercial motor vehicle unless he/she is physically qualified to do so and, except as provided in §391.67 (Farm vehicle drivers of articulated commercial motor vehicles), has on his/her person the original, or a photographic copy, of a medical examiner's certificate that he/she is physically qualified to drive a commercial motor vehicle.

(b) A person is physically qualified to drive a commercial motor vehicle if that person —

(b)(3) Has no established medical history or clinical diagnosis of diabetes mellitus currently requiring insulin for control.

As stated above (§391.41(b)(3)), U.S. law currently prohibits individuals with insulin-treated diabetes from driving a CMV in interstate commerce. However, it should be noted that §391.64 (grandfathering for certain drivers participating in diabetes waiver study programs) states that the provisions of §391.41(b)(3) do not apply to a driver who was a participant in good standing on March 31, 1996 and in a waiver study program on the operation of CMVs by insulin-controlled diabetic drivers provided that the following conditions are met:

(a)(1) The driver submits to a physical examination every year, including an examination by a board-certified/eligible endocrinologist attesting to the fact that the driver is:

(a)(1)(i) Otherwise qualified under §391.41;

(a)(1)(ii) Free of insulin reactions (an individual is free of insulin reactions if that individual does not have severe hypoglycemia or hypoglycemia unawareness, and has less than one documented, symptomatic hypoglycemic reaction per month);

(a)(1)(iii) Able to and has demonstrated willingness to properly monitor and manage his/her diabetes; and

(a)(1)(iv) Not likely to suffer any diminution in driving ability due to his/her diabetic condition.

(a)(2) The driver agrees to and complies with the following conditions:

(a)(2)(i) A source of rapidly absorbable glucose shall be carried at all times while driving;

(a)(2)(ii) Blood glucose levels shall be self-monitored one hour prior to driving and at least once every four hours while driving or on duty prior to driving using a portable glucose monitoring device equipped with a computerized memory;

(a)(2)(iii) Submit blood glucose logs to the endocrinologist or medical examiner at the annual examination or when otherwise directed by an authorized agent of the FMCSA;

(a)(2)(iv) Provide a copy of an endocrinologist's report to the medical examiner at the time of the annual medical examination; and

(a)(2)(v) Provide a copy of an annual medical certification to the employer for retention in the driver's qualification file and retain a copy of the certification on his/her person while driving for presentation to a duly authorized Federal, State or local enforcement official.

Brief History of CMV Driver and Diabetes Policy

Beginning January 1, 1940, the Interstate Commerce Commission's Motor Carrier Safety Regulations (4 FR 2294) began requiring CMV operators to undergo urine glucose testing as part of medical examinations to evaluate whether they were qualified to engage in driving for the purposes of interstate or foreign commerce.(48) The current standard for diabetes was established on January 1, 1971 (35 FR 6458) in response to several risk assessment studies suggesting that diabetic drivers had a higher rate of accident involvement than the general population. On March 28, 1977 comments on proposed changes to this standard were solicited via the Advance Notice of Proposed Rulemaking (ANPRM 42 FR 16452): the prohibition was maintained after a consideration of the comments and the current literature, citing concerns over highway safety (Nov. 1977).(49)

On November 25, 1986 a new AMPRM (52 FR 45204) was issued requesting comments on petitions from two individuals and the American Diabetic Association to eliminate blanket prohibitions on insulin-using CMV drivers, with waivers to be granted to qualified drivers with insulin-treated diabetes on a case-by-case basis. The Conference on Diabetic Disorders and Commercial Drivers (September 1987) was convened to review the diabetes standard in light of new developments in the treatment of diabetics. Conference participants (physicians, scientists, federal officers, and representatives from the motor carrier industry) recommended that waivers could be granted to some drivers depending on conditions such as insulin use, absence of recurrent hypoglycemia, and a safe driving record (Federal Highway Administration, Conference on Diabetic Disorders and Commercial Drivers; Final Report, 1988).(50) In 1990, a Notice of Proposed Rulemaking (55 FR 41208) soliciting comments on a proposal to revise the diabetes standard to allow insulin-treated individuals to operate CMVs if they met certain criteria and

were found qualified by an endocrinologist. A risk assessment study performed by Carnegie Mellon University and the University of Pittsburgh estimating the various levels of accidents among diabetic drivers depending on the severity of hypoglycemia was sponsored in conjunction with the Notice of Proposed Rulemaking. The study estimated that an additional 42 crashes would occur each year if the insulin ban was lifted.(51) This increase was considered acceptable and a Notice of Intent to Issue Waivers was released in 1992.

A diabetes waiver program was established in 1993 as part of a research study to investigate whether drivers with insulin-treated diabetes admitted to the program could safely operate CMVs. Participating drivers were required to have a minimum of three years of recent CMV driving experience while using insulin, a safe driving record, and certification by an endocrinologist and an ophthalmologist. The waiver program was set to last for three years, or until resolution of the concurrent rulemaking action, whichever occurred first.

In 1996 the District of Columbia Court of Appeals ruled in *Advocates for Highway and Auto Safety versus Federal Highway Administration* that a vision waiver program was contrary to law in that it "was devoid of empirical support in the record" (meaning that the initial determination that the vision waiver program would not adversely affect the safe operation of CMV was not defensible through data). Since the diabetes waiver program used a similar approach to pre-qualification of drivers as the vision waiver program, it too was terminated. Drivers then holding a diabetes-related waiver were allowed, under 'grandfather' provisions (49 CFR 391.64), to continue to operate CMVs in interstate commerce.

The Transportation Equity Act for the 21st Century (June 9, 1998, TEA-21; Pub. L. 105-178, 112 Stat. 107) directed an inquiry into the feasibility of developing a safe and practical program for allowing individuals with insulin-treated diabetes to operate CMVs interstate.(52) This inquiry was required to evaluate research and other relevant information on the effects of insulin on driving performance, consult with individual state programs for CMV operation by drivers with insulin-treated diabetes, evaluate the Department of Transportation's (DOT) policies in other modes of transportation, analyze pertinent risk data, consult with interested groups knowledgeable about diabetes and related issues, and assess the possible legal ramifications of permitting individuals with insulin-treated diabetes to operate CMVs in interstate commerce. The findings of this inquiry were to be reported to Congress, along with the elements of a protocol to permit individuals with IDDM to operate CMVs (should such a program prove feasible). In addition, TEA-21 provided for the administration of waivers and exemptions for persons seeking regulatory relief from statutes governing insulin-treated diabetes and CMV interstate operation. Depending on the nature of the request, these waivers and two-year exemptions (49 U.S.C. 31315 and 31136[e]) were required to go through a period of public comment via release in the *Federal Register*.

The results of the report authorized under TEA-21 were submitted to Congress on August 23, 2000 with the conclusion that a safe and practicable protocol to allow some IDDM individuals to operate CMVs was feasible. The report included a then-current review of the literature on the risk of driving with diabetes.(53) As the literature review detailed, there was no consistent trend in the risk of automobile crashes related to diabetes, although many studies suffered from flawed methodology, and none directly addressed CMV operation.

Federal Motor Carrier Safety Administration (FMCSA) published a notice of intent to issue exemptions to insulin-dependent diabetes mellitus CMV drivers in the *Federal Register* on

July 31, 2001 (66 FR 39548). On September 3, 2003 FMCSA began accepting applications from qualified CMV drivers with insulin-treated diabetes to request an exemption from the regulations of 49 CFR 391.41[b][3].(54) The duration of the exemption was limited to two years and could be renewed. The exemption could be immediately revoked if: the person failed to comply with the terms and conditions of the exemption; the exemption resulted in a lower level of safety than was maintained before the exemption was granted; or if continuation of the exemption was inconsistent with the goals and objectives of the regulations issued under the authority of 49 U.S.C. 31315 and 31136[e]. FMCSA did not amend its diabetes standard.

The 2003 FMCSA diabetes exemption process had three components. The first was a screening component to identify qualified applicants. This process examined the applicant's experience and safety in operating CMVs with insulin-treated diabetes, history of hypoglycemia, and the results of examinations by medical specialists. One important requirement in the screening process was that applicants should have three years of safe CMV driving experience while using insulin. The second component provided guidelines for managing diabetes while operating a CMV, including supplies to be used and the protocol for monitoring and maintaining appropriate blood glucose levels. The last component specified FMCSA's process for monitoring insulin-treated commercial drivers. The specifications addressed the required medical examinations and the schedule for their submission. In addition, these specifications indicated how glucose measures should be taken and reviewed, and how episodes of severe hypoglycemia and accidents should be reported.

Since that exemption program began in 2003, FMCSA received 154 applications, and had granted exemptions in five cases. The remaining 149 cases were pending as of November 2005. Exemption denials have clustered into three groups, according to FMCSA: applicants with limited driving experience, insufficient length of time documenting the medical condition, and poor driving records.(55)

On February 12, 2004 the Senate Highway Funding Bill–Truck Safety Provisions Sec. 4229 (Anti-Safety Provision)–announced the following decisions in the section entitled *Operation of Commercial Motor Vehicles by Individuals who Use Insulin to Treat Diabetes Mellitus*:

- Directed the Secretary to issue a rule to provide for individual assessments of commercial driver's license (CDL) applicants who use insulin to treat diabetes;
- Statutorily exempted diabetic drivers from current medical requirements and from need to make application to FMCSA diabetes exemption program;
- Stated the rule may require CDL applicants with diabetes to have used insulin for a minimum period of time and to demonstrate stable control of their diabetes;
- Eliminated the requirement that CDL applicants with diabetes have previous experience driving a CMV.(56)

Safe, Accountable, Flexible and Efficient Transportation Equity Act: A Legacy for Users (SAFETEA-LU), of August 2005 required FMCSA to revise the terms and conditions used to issue exemptions to certain insulin-treated diabetic drivers of CMVs from the diabetes mellitus prohibitions contained in the FMCSRs. Drivers with insulin-treated diabetes mellitus (ITDM) who met the modified criteria were able request an exemption from 49 CFR 391.41(b)(3).(57)

The issue of diabetes mellitus and CMV operator qualifications was revisited in the November 8, 2005 *Federal Register* (Vol. 70, Number 125), which announced a revision of the terms and conditions of its previous decision to issue exemptions to certain CMV drivers with insulin-treated diabetes. These revisions were in response to section 4129 of SAFETEA-LU, which required FMCSA to modify its exemption program to allow individuals who use insulin to treat diabetes mellitus to operate CMVs in interstate commerce without having to demonstrate safe driving experience operating a CMV while using insulin, while at the same time implementing certain other requirements in section 4129.(58)

As required by section 4129(b)(c), these changes are: (1) elimination of the requirement for three years of experience operating CMVs while being treated with insulin; and (2) establishment of a specified minimum period of insulin use to demonstrate stable control of diabetes before being allowed to operate a CMV. In addition, Section 4129(d) directed FMCSA to ensure that drivers with insulin-treated diabetes would not be held to a higher standard than other drivers, with the exception of limited operating, monitoring, and medical requirements deemed medically necessary.

On March 17, 2006, FMCSA published an Advance Notice of Proposed Rulemaking (ANPRM docket number FMCSA 2005-23151) to begin a reevaluation of the rule that prohibits drivers with insulin-treated diabetes from operating CMVs. Public comments and the advice of the newly appointed Medical Review Board were considered in the evaluation of potential changes to the existing medical standards. The deadline for comment submission was June 15, 2006.(48)

Current State Regulatory Criteria for CMV Drivers

As stated at the beginning of *Current Federal Regulatory and Medical Advisory Criteria for CMV Operators* section, motor carriers engaged purely in intrastate commerce are not directly subject to FMCSRs, found in 49 CFR 301 through 399 regulations. State regulations for intrastate motor carriers must be identical to, or compatible with the Federal regulations in order for States to receive motor carrier safety grants from FMCSA.(59)

There are wide disparities in intrastate medical waiver programs across the United States. Overall, 26 states will consider issuing a waiver for IDDM if the CMV driver has a good safety record and agrees to added restrictions and monitoring. In 23 states there are no waivers for CMV drivers with insulin-treated diabetes. Alaska has no physical examination requirement for commercial drivers. Table 5 lists diabetic waivers for CMV drivers with insulin-treated diabetes by state as of January 2000.(60)

Table 5. Diabetic Waivers by State

State	Waiver – Yes, No, NA	State	Waiver – Yes, No, NA	State	Waiver – Yes, No, NA
Alabama	No	Kentucky	Yes	North Dakota	No
Alaska	NA	Louisiana	No	Ohio	No
Arizona	No	Maine	No	Oregon	Yes
Arkansas	No	Maryland	No	Pennsylvania	Yes
California	Yes	Massachusetts	Yes	Rhode Island	Yes
Colorado	Yes	Michigan	Yes	South Carolina	No
Connecticut	Yes	Minnesota	Yes	South Dakota	No
DC	No	Mississippi	No	Tennessee	Yes
Delaware	Yes	Missouri	No	Texas	No
Florida	Yes	Montana	Yes	Utah	Yes
Georgia	No	Nebraska	No	Vermont	Yes
Hawaii	No	Nevada	Yes	Virginia	Yes
Idaho	No	New Hampshire	Yes	Washington	Yes
Illinois	No	New Jersey	No	West Virginia	Yes
Indiana	No	New Mexico	Yes	Wisconsin	Yes
Iowa	No	New York	Yes	Wyoming	Yes
Kansas	Yes	North Carolina	Yes		

Non-U.S. Licensing

For purposes of comparison, a table delineating the licensing of CMV drivers with insulin-treated diabetes in selected foreign countries is included below (Table 6).

Table 6. Licensing of CMV Drivers with Insulin Treated-Diabetes in Foreign Countries

Are Individuals with insulin-treated diabetes free to drive a CMV?		
Yes	**Yes, with special requirements**	**No**
Argentina	Australia	Czech Republic
Brazil	Austria	Greece
Japan	New Zealand	Italy
Tanzania	United Kingdom	Mexico
Thailand	Chile	Poland
		Sweden

As in the United States, there is considerable variability in the special requirements used to allow an individual with insulin-dependent diabetes mellitus to obtain a commercial driver's license.

Treatment by Individual States of CMV Drivers with IDDM

Reflecting the option to apply the FMCSRs to medical qualifications of intrastate operators of CMVs, individual states vary widely in how they deal with CMV drivers with insulin-treated diabetes. As demonstrated in the table above, states vary in whether they allow drivers with insulin-treated diabetes to operate CMVs. Other states have 'grandfathered' drivers who were operating a CMV, while disallowing new drivers with insulin-treated diabetes to obtain a CDL. The Association for the Advancement of Automotive Medicine (1997) and the American Diabetes Association (1997) conducted surveys of state practices in regard to CMV drivers with insulin-treated diabetes. Below is a brief summary of the results submitted by states participating in these surveys.(59)

Alabama

The state of Alabama follows the FMCSRs and does not allow IDDM individuals to obtain a waiver from the requirements. CMV drivers with insulin-treated diabetes who practiced before the ruling are 'grandfathered.'

California

In the past, California issued restricted licenses to intrastate CMV drivers with insulin-treated diabetes who did not meet FMCSA standards, but in general, the licensing of these individuals is rare. The restricted license may include a scope of employment restriction specific to the individual's current job, restrictions against transporting hazardous materials or operation of vehicles requiring a passenger endorsement. Drivers with insulin-treated diabetes who receive a restricted license are generally diabetics who initially controlled the disease with oral drugs and have progressed to insulin use.

Delaware

Delaware only restricts CMV drivers with insulin-treated diabetes from operating vehicles in excess of 26,000 lbs., with no restrictions on drivers of CMVs between 10,001 and 25,999 lbs. Waivers are not permitted for CMV drivers with insulin-treated diabetes to operate vehicles that transport passengers or hazardous materials.

Hawaii

Hawaii follows the FMCSRs and currently allows drivers with insulin-treated diabetes, provided they otherwise qualify for a commercial driver's license (CDL) and qualify under rules regulating IDDM adopted by the State Legislature (2002).

Illinois

Illinois currently allows CMV drivers with insulin-treated diabetes who have been eligible, licensed, and operating a CMV prior to July 29, 1986 to operate CMVs with a gross vehicle weight rating (GVWR) or gross combination weight rating (GCWR) of 12,001 lbs. or more. Illinois also allows CMV drivers with insulin-treated diabetes to operate under restriction.

Kansas

Kansas follows the FMCSRs for drivers transporting passengers in a vehicle that is not owned by a city or county. These drivers must also carry a medical card that certifies their fitness to drive. Kansas Statute 66-1,129 (c) excludes motor vehicles owned and operated by..."any municipality or any other political subdivisions of this state." In addition, in Kansas there is no process for a diabetes waiver for CDL drivers with a passenger endorsement

Kentucky

Kentucky issues medical waivers for CMV drivers with insulin-treated diabetes not meeting certain FMCSA standards. Waiver applications include a completed medical examination form and supplemental medical form. Other factors considered in the waiver application include driving record, uncontrolled diabetes, and a history of diabetic shock or coma.

Maryland

In 2001, Maryland discontinued a pilot program providing waivers for drivers with insulin-treated diabetes due to safety concerns, a lack of guidelines in place for glucose monitoring while performing transportation duties, and concerns about physician education about requirements for drivers with insulin-treated diabetes.

Michigan

Michigan allows medical waivers to be issued with the following requirements: a medical and driving history, medical evaluation by the operator's personal physician, self-monitoring of blood glucose concentrations, and biannual reevaluation by a specialist. In addition, operators over 40 years of age are required to pass a maximal exercise stress test.

New York

New York allows CMV drivers with insulin-treated diabetes to operate buses with proof that the operator has been free of incidents of hyperglycemia or hypoglycemia shock in the past two years. The operator must be under medical supervision, with written certification provided by the physician biannually. CMV drivers with insulin-treated diabetes who do not drive buses are not regulated unless they suffer a loss of consciousness; those who suffer such an incident are subject to regulations and may have to be incident-free to continue driving prior to agency approval.

Oregon

Oregon has provided limited exemptions and waivers for CMV drivers with insulin-treated diabetes since 1984. The exemptions and waivers are subject to medical requirements.

Texas

Texas does not issue exemptions for CMV drivers with insulin-treated diabetes.

Utah

Utah allows medical waivers to be issued with the following requirements: an extensive medical history check for the past five years, a driving record check, a complete medical examination by

an internist or endocrinologist, on-going monitoring and reevaluation requiring self-testing and recording of results by the CMV operator. The waiver must be renewed either annually or biannually on the recommendation of the operator's health care professional.

Wisconsin

Wisconsin allows CMV drivers with insulin-treated diabetes to operate if they have certification of qualification from two physicians. Drivers are also subject to a two-year follow-up review.

Methods

The *Methods* section provides a synopsis of how we identified and analyzed information for the report. The section briefly covers the key questions addressed, literature searches performed, the criteria used, including studies, evaluation of study quality, assessment of the strength of the evidence base for each key question, and the methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, statistical approaches used, etc., are documented in appendices.

Key Questions

This evidence report addresses four key questions. These key questions, which were developed by FMCSA in collaboration with ECRI, are listed below:

Key Question 1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?

In addressing this question we examine the relationship between hypoglycemia and the following direct and indirect outcome measures:

a) *Simulated driving performance (indirect)*
b) *Driving-related cognitive and psychomotor performance (indirect)*

Key Question 3: What treatment-related factors are associated with an increased incidence of severe hypoglycemia among individuals with diabetes mellitus?

Potential factors to be assessed in addressing this question include the following:

a) *Mechanism of glycemic control (insulin, 1st generation[7] sulfonylureas, 2nd generation[8] sulfonylureas, meglitinides, and other hypoglycemic drugs used to control blood glucose levels)*
b) *Route of insulin administration (inhaled, subcutaneous injection, pump)*

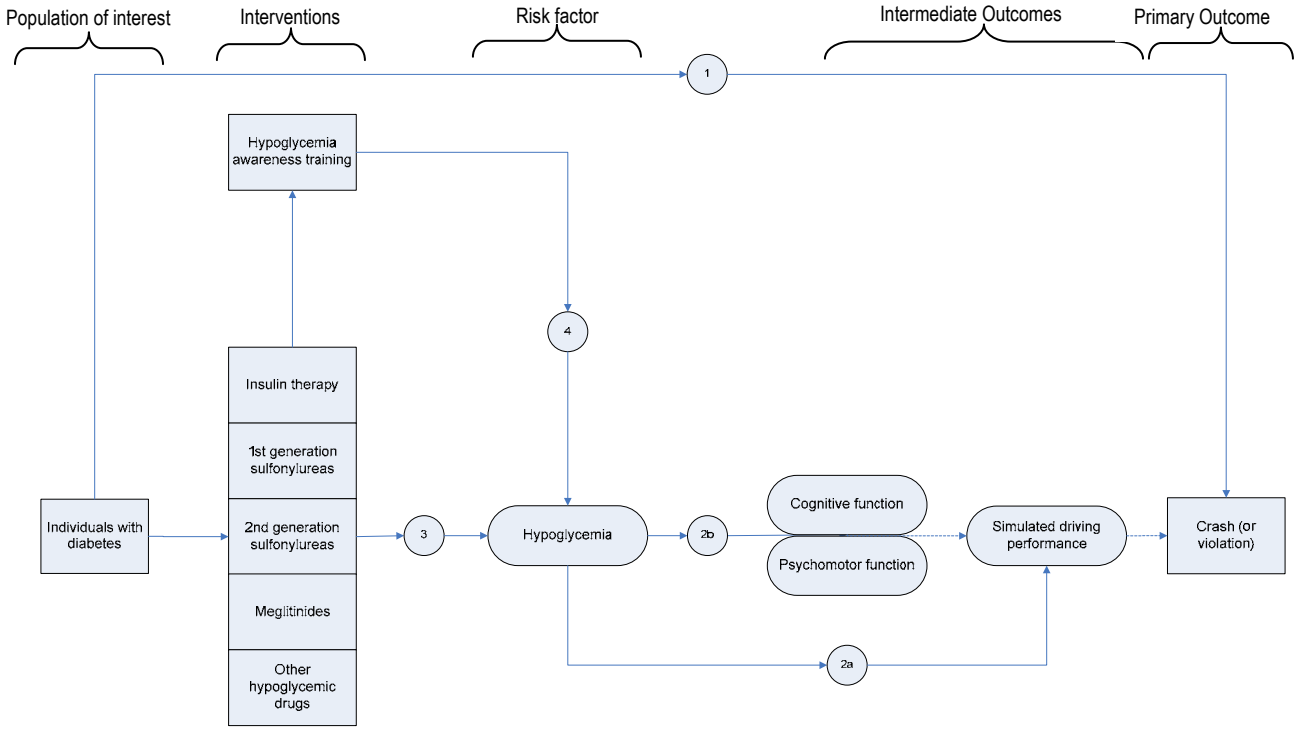
Key Question 4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

The key questions above are put into context by the logic framework presented in Figure 2. The logic framework shows the logical relationships between the population of interest, the risk factors of interest, interventions of interest, intermediate outcome, and the outcome of primary importance; crash risk.

The numbered lines in the framework map onto the key questions that we expect to address in this report. We note that the strength of the relationship between intermediate outcome (hypoglycemia) and the primary outcome (crash) can be influenced by a number of modifiable determinants. Modifiable determinants are variables that affect the pathway and each other and include the following: other personal risk factors (e.g., hours of sleep the previous night), vehicle risk factors (e.g., brake adjustment), environmental factors (e.g., weather and roadway features), and risks created by other drivers and traffic.

[7] 1st generation sulfonylureas include: tolbutamide, acetohexamide, tolazamide, chloropropamide.
[8] 2nd generation sulfonylureas include: glipizide, glyburide, glimepiride

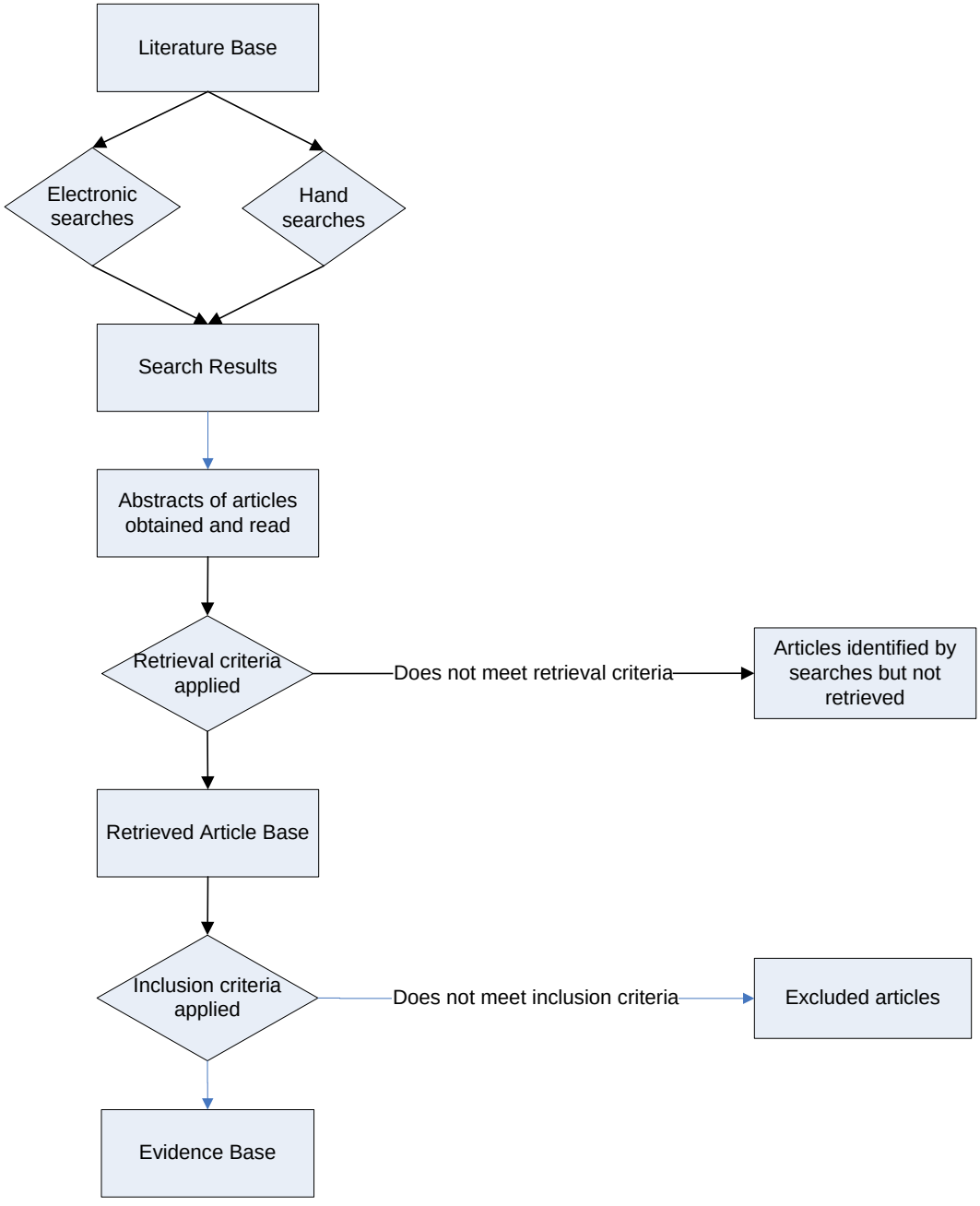
Figure 2. Logic Framework



Identification of Evidence Bases

The individual evidence bases for each of the key questions addressed in this evidence report were identified using the multistaged process captured by the algorithm presented in Figure 3. The first stage of this process consists of a comprehensive search of the literature. Searches were conducted by ECRI's information specialists. The second stage of the process consists of the examination of abstracts of identified studies in order to determine which articles would be retrieved. The final stage of the process consists of the selection of the actual articles that will be included in the evidence base.

Figure 3. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews, which use a less rigorous approach to identifying and obtaining literature, thereby allowing a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias because we obtain and include articles according to explicitly determined *a priori* criteria. Full details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 7.

Table 7. Electronic Databases Searched

Name of database	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 10, 2006	OVID
Cochrane Library	Through 2006 Issue 2	www.thecochranelibrary.com
Embase (Excerpta Medica)	1980 through April 28, 2006	OVID
Medline	1966 through May 19, 2006	OVID
PubMed (Pre Medline)	Premedline[sb] last searched April 28, 2006	www.pubmed.gov
PSYCH Info	Through April 28, 2006	http://www.apa.org/psycinfo/
TRIS Online (Transportation Research Information Service Database)	Through April 28, 2006	http://trisonline.bts.gov/search.cfm

Manual Searches

We reviewed journals and supplements maintained in ECRI's collections of more than 1,000 periodicals. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant reports not identified by our electronic searches. In order to retrieve additional relevant information, we also performed hand searches of the "gray literature." Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These latter documents do not appear in the peer-reviewed journal literature.

Identification of Ongoing Trials

The identification of ongoing trials is important because when a systematic review is later updated, the status of ongoing trials can be assessed for possible inclusion. Currently, no single central register of ongoing trials exists. Instead, there are hundreds of distinct, predominantly online registers that vary widely in content, quality, and accessibility. Various efforts have been made by independent groups to begin to provide central access to ongoing trials, mostly through Web sites that provide links to hundreds of registers of ongoing clinical trials. Two such

examples are TrialsCentral™ (www.trialscentral.org) and Current Controlled Trials (www.controlled-trials.com). Current Controlled Trials also has a searchable database of information about thousands of ongoing and completed trials, including those registered on ClinicalTrials.gov (www.clinicaltrials.gov).

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions about whether a full-length article should be retrieved are usually based on a review of available abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with FMCSA. These retrieval criteria are presented in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If it was unclear whether a potentially relevant article met our retrieval criteria (e.g., no abstract was available for evaluation), the full-length version of that article was be obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI analyst who determined whether that article met a set of predetermined, question-specific, inclusion criteria. As was the case for the retrieval criteria, the inclusion and exclusion criteria for this evidence report were determined *a priori* in conjunction with FMCSA. These inclusion and exclusion criteria are presented in Appendix C.

If on reading an article it was found not to meet the question-specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the reason(s) for its exclusion, is presented in Appendix D.

Evaluation of Quality of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focused on the overall *body* of the available evidence that was used to draw an evidence-based conclusion. Using this approach, which is described in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, we will also consider the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g., Individuals with diabetes who require insulin are at increased risk for a motor vehicle accident) and a quantitative conclusion (e.g., When compared with individuals without diabetes, the relative risk for a motor vehicle crash among individuals with diabetes who require insulin is 1.37; 95% CI: 1.03–1.74; P <0.005). As shown in Table 8, we assigned a separate strength-of-evidence rating to each of type of conclusion. Evidence underpinning a qualitative conclusion was rated according to its strength, and evidence underpinning quantitative conclusions was rated according to the stability of the effect size estimate that was calculated.

Table 8. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Weak	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Unacceptably Weak	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect size estimates that are deemed to be stable are more unlikely to change significantly with the publication of new data than are unstable effect size estimates.

Statistical Methods

The set of analytic techniques used in this report was extensive (Appendix B). In summary, random- and fixed-effects meta-analyses were used to pool data from different studies.(1-4,61,62) Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2.(5-7,61,63-65) Whenever appropriate, heterogeneity was explored using meta-regression techniques.(66-68) Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative fixed- and random-effects meta-analyses.(8-10,69-72) The presence of publication bias was tested for using the "trim and fill" method.(11-13,73)

We calculated several different estimates of treatment effectiveness. The choice of effect size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. Between-group differences in outcome measured using continuous data were analyzed in their original metric (if all included studies reported on the same outcome using the same metric) or the data were standardized into a common metric known as the standardized mean difference (SMD). Dichotomous data were analyzed using the risk ratio (RR) or the odds ratio (OR). The formulae for all four of these effect sizes and their variances are presented in Table 9. If means and standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from

reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(74)

Table 9. Effect Size Estimates and their Variance

Effect size	Formula (Effect size)	Formula (Variance)
Original metric	$\mu_{TG}-\mu_{CG}$	$\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)\left(\frac{1}{n_{TG}}+\frac{1}{n_{cg}}\right)$
SMD	$\frac{\mu_{TG}-\mu_{CG}}{\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}}+\frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} = mean (treatment group); μ_{CG} = mean (control group); S_{TG} = standard deviation (treatment group); S_{CG} = standard deviation (control group); n_{TG} = enrollees (treatment group); n_{CG} = enrollees (control group)		
RR	$\frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)}=\frac{a(c+d)}{c(a+b)}$	$\frac{1}{a}+\frac{1}{a+b}+\frac{1}{c}+\frac{1}{c+d}$
Where: a = number of individuals with diabetes who crashed; b = number of individuals with diabetes who did not crash; c = number of individuals without diabetes who crashed; d= number of individuals without diabetes who did not crash.		
OR	$\frac{\left(\frac{a}{b}\right)}{\left(\frac{c}{d}\right)}=\left(\frac{ad}{bc}\right)$	$\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$
Where: a = number of individuals with diabetes who crashed; b = number of individuals without diabetes who crashed; c = number of individuals with diabetes who did not crash; d= number of individuals without diabetes who did not crash.		

Synthesis of Results

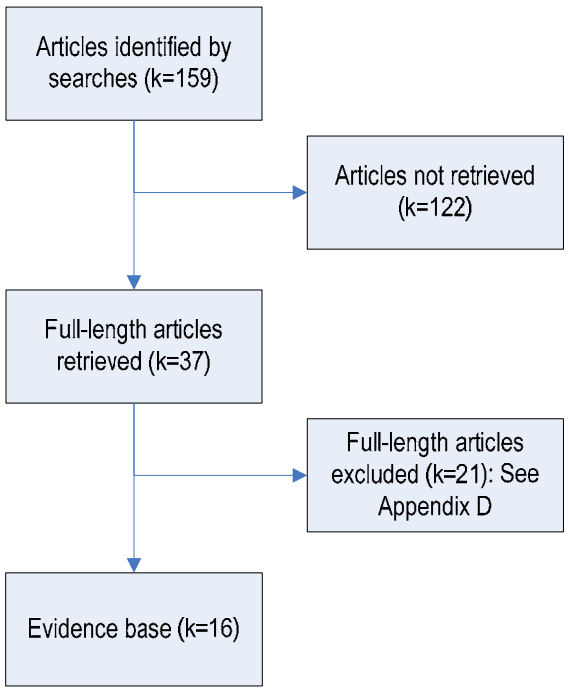
This section summarizes the findings of our analyses for each of the four key questions that we addressed.

***Key Question 1:* Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?**

Identification of Evidence Base

The identification of the evidence base for Key Question 1 is summarized in Figure 4. Our searches[9] identified a total of 159 articles that appeared relevant to this key question. Following application of the retrieval criteria[10] for this question, 37 full-length articles were retrieved and read in full. Of these 37 retrieved articles, 16 articles were found to meet the inclusion criteria[11] for Key Question 1. Table D-1 of Appendix D lists the 21 articles that were retrieved but then excluded and provides rationale for their exclusion. Table 10 lists the 16 articles that met the inclusion criteria for Key Question 1. Complete descriptions of the studies included in the evidence base for this question are presented in *Study Summary Tables* in Appendix G.

Figure 4. Development of Evidence Base for Key Question 1



[9] See Appendix A for search strategies
[10] See Appendix B for retrieval criteria
[11] See Appendix C for inclusion criteria

Table 10. Evidence Base for Key Question 1

Reference	Year	Study Location	Country
Cox et al.(40)	2003	Boston, Charlottesville, Chicago, Indianapolis, Louisville, St. Louis, Syracuse in USA Amsterdam, Basel, Edinburgh and Mergentheim in Europe	USA, Germany, Netherlands, Scotland, and Switzerland
Laberge-Nadeau et al.(75)	2000	Quebec	Canada
McGwin et al.(76)	1999	Alabama	USA
Gressert et al.(77)	1994	Quebec	Canada
Koepsell et al.(78)	1994	Washington	USA
De Klerk et al.(79)	1993	Western Australia	Australia
Hansotia et al.(80)	1991	Wisconsin	USA
Stevens et al.(42)	1989	Belfast	Northern Ireland
Eadington et al.(43)	1988	Edinburgh	Scotland
Songer et al.(44)	1988	Pennsylvania	USA
Davis et al.(81)	1973	Oklahoma	USA
Ysander et al.(82)	1970	Gothenburg	Sweden
Campbell et al.(83)	1969	Prince Edward Island	Canada
Crancer et al.(84)	1968	Washington	USA
Ysander et al.(85)	1966	Stockholm	Canada
Waller et al.(86)	1965	California	USA

Evidence Base

This subsection provides a brief description of the key attributes of the 16 studies that comprise the evidence base for Key Question 1. Here we discuss applicable information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 11.

Table 11. Key Study Design Characteristics of Studies that Address Key Question 1

Reference	Year	Design	Comparison	Driving exposure controlled for?	Primary outcome	Definition of crash	Outcome self-reported?
Cox et al.(40)	2003	Case-Control Study†	673 individuals with diabetes compared with 363 individuals without diabetes	Yes	Difference in crash rate	Any motor vehicle accident where enrollee was driver	Yes (questionnaire)
Laberge-Nadeau et al.(75)	2000	Case-Control Study†	4,495 individuals with diabetes compared with 8,958 individuals without diabetes	Yes	Difference in crash rate	CMV driver crash where enrollee was driver	No (provincial records)
McGwin et al.(76)	1999	Case-control study*	249 individuals at-fault crash compared with 454 individuals no-crash	Yes	Difference in proportion of individuals with diabetes	At-fault crash where enrollee was driver	Yes (Telephone questionnaire)
Gressert et al.(77)	1994	Case-control study*	1,400 individuals injurious crash compared with 2,636 individuals no-crash	Yes	Difference in proportion of individuals with diabetes	Non-fatal crashes with minor bodily injury (not requiring hospitalization)	No (provincial records)
Koepsell et al.(78)	1994	Case-control study	234 individuals injured in crash compared with 446 not involved in crash	Yes	Difference of proportion of individuals with diabetes	Injurious motor vehicle crash where enrollee was driver	No (Health insurance and police records)
De Klerk et al.(79)	1993	Case-Control Study†	8,623 individuals with diabetes compared with Expected rates from entire population of Western Australia	No	Difference in crash rate	Injurious motor vehicle crash where enrollee was driver	No (hospital records)
Hansotia et al.(80)	1991	Case-Control Study†	484 individuals with diabetes compared with 30,420 individuals without diabetes	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	No (State Records)
Stevens et al.(42)	1989	Case-Control Study†	354 individuals with diabetes compared with 307 individuals without diabetes	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	Yes
Eadington et al.(43)	1988	Case-Control Study†	187 individuals with diabetes compared with Accident rate data obtained from Department of Transport Statistics and insurance claims	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	Yes
Songer et al.(44)	1988	Case-Control Study†	127 individuals with diabetes compared with 127 individuals without diabetes	Yes	Difference in crash rate	Any motor vehicle accident where enrollee was driver	Yes

Reference	Year	Design	Comparison	Driving exposure controlled for?	Primary outcome	Definition of crash	Outcome self-reported?
Davis et al.(81)	1973	Case-Control Study†	108 individuals with diabetes compared with 1,650,245 non-diabetics	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	No (state records)
Ysander(82)	1970	Case-Control Study†	219 individuals with diabetes compared with 219 individuals without diabetes	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	No (state records)
Campbell et al.(83)	1969	Case-Control Study†	346 individuals with diabetes compared with 346 individuals without diabetes	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	No (Provincial Records)
Crancer et al.(84)	1968	Case-Control Study†	7,646 individuals with diabetes compared with 1,600,000 individuals without diabetes	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	No (state records)
Ysander(85)	1966	Case-Control Study†	256 individuals with diabetes compared with 256 individuals without diabetes	No	Difference in crash rate	Injurious motor vehicle crash where enrollee was driver	No (Government Records)
Waller et al.(86)	1965	Case-Control Study†	287 individuals with diabetes compared with 922 individuals without diabetes	No	Difference in crash rate	Any motor vehicle accident where enrollee was driver	No (state records)

*A case-control study in which cases are defined according to whether individuals have experienced a crash and controls consist of a cohort of individuals who have not.

†A case-control study in which cases are defined according to the presence of diabetes and controls consist of a cohort of individuals who do not.

‡Study utilized "induced exposure method," which has been proposed as a case-control approach to estimate relative risk in the absence of exposure data. Rationale is that the crash involvement of not at fault drivers (controls) is directly proportional to their exposure, and the prevalence of a given risk factor among controls is a good proxy for the prevalence in the driving population at large.

None of the 16 included studies that addressed Key Question 1 were prospective. All of the included studies used one of two different case-control methodologies. The most commonly used methodology (*k=13*) was to select drivers with diabetes (cases) and compare their risk with that of drivers not having the condition. The alternative, less commonly used (*k=3*) approach was to select cohorts on the basis of crash involvement and compare the prevalence of diabetes among individuals who experienced a crash (cases) and those who did not (controls).

A design problem common to many risk assessment studies is the failure to control adequately for exposure. In this instance, the exposure variable of critical importance is the number of miles driven per unit time. If cases and controls are not well matched for exposure, then observed differences in risk may simply be the consequence of differences in exposure. Several of the studies in the present evidence base controlled for exposure by either ensuring that driving patterns in cases and controls were well matched or by adjusting crash risk data for differences in exposure using regression techniques.(40,44,75-78,87)

Most included studies assessed the risk of diabetes associated with any motor vehicle accident in which the involved individual was a driver. However, some heterogeneity in the definition of a crash does exist between the studies. McGwin et al.(76) analyzed crash data for individuals who were deemed to be "at fault" in the accident. Koepsell et al.,(78) Ysander,(85) and De Klerk et al.(79) focused their attention on the risk for an injurious motor vehicle crash.

Crash data from which crash rates were determined were obtained from two primary sources; databases and questionnaires. In order for data from databases to be informative, relevant information contained within it must be precise. Since we have no way of determining how precise the information contained within any of the databases used to inform the studies included in this report are, the degree of confidence that one may have in data extracted from these databases is not clear. The degree of confidence that one can have in crash rates derived from questionnaires is also unclear, primarily because questionnaires depend upon the honesty of the individual being questioned.

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Question 1 are presented in Table 12. This assessment found that the quality of the included studies was not high. Four of the 16 included studies were graded as moderate quality. The remaining 12 studies were graded as low quality. Note that even though some studies scored highly, these studies used a case-control study design. Case-control studies, by virtue of their retrospective design, are susceptible to bias, meaning that even a perfectly designed and executed case-control study cannot be graded as high quality. Other factors that differentiated moderate from low quality studies included poor reporting and, in many cases, a failure to adjust for exposure differences in cases and controls.

Table 12. Quality of that Assess Key Question 1

Reference	Year	Quality Scale Used	Quality Score	Quality
Cox et al.(40)	2003	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	8.5	Moderate
Laberge-Nadeau et al.(75)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	9.4	Moderate
McGwin et al.(76)	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	10.0	Moderate
Gressert et al.(77)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	7.8	Low
Koepsell et al.(78)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	9.4	Moderate
De Klerk et al.(79)	1993	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	6.3	Low
Hansotia et al.(80)	1991	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	5.4	Low
Stevens et al.(42)	1989	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	7.0	Low
Eadington et al.(43)	1988	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	7.7	Low
Songer et al.(44)	1988	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	7.9	Low
Davis et al.(81)	1973	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	5.8	Low
Ysander et al.(82)	1970	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	8.1	Moderate
Campbell et al.(83)	1969	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	6.5	Low
Crancer et al.(84)	1968	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	4.2	Low

Reference	Year	Quality Scale Used	Quality Score	Quality
Ysander et al.(85)	1966	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	7.1	Low
Waller et al.(86)	1965	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	7.1	Low

Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that address Key Question 1 are presented in Table 13. The information included in this table demonstrates that currently available data that is directly generalizable to CMV drivers is extremely limited; only one included study evaluated crash risk in this group of drivers.(75) The remaining 15 studies included individuals who held private motor vehicle licenses. No doubt, included among these individuals were some CDL holders; however, the exact proportion of such drivers cannot be determined.

The generalizability of the findings of these are limited by the lack of data specific to CMV drivers with diabetes and include the following factors:

- Exposure levels are lower than would be seen in a CMV driver population. This will most likely lower the risk for a motor vehicle crash among the individuals included in the majority of the included studies.
- The proportion of women in the study samples are higher than would be seen in a CMV driver population.
- Three included studies were designed to determine the crash risk among elderly (aged >65 years) diabetics.(76-78) Note that we did not exclude these studies from our analyses because there is no upper age limit to being able to drive a CMV.[12] Also, inclusion of such studies gave us the potential for investigating the interaction between aging and diabetes and their combined influence on crash risk.

[12] Because these studies may represent a specific subgroup of studies we ensured that we repeated our primary analysis with these studies removed as part of a series of sensitivity analysis (see below).

Table 13. Individuals with Diabetes Enrolled in Studies that Address Key Question 1

Reference	Year	Type of diabetes	(number of individuals with diabetes included (n=)	Age distribution	Duration of diabetes	% Male	% CMV drivers	Driving exposure	% white	Generalizability to target population
Cox et al.(40)	2003	type 1/type 2	673	Mean (T1)=42.4 yrs. Mean (T2)=56.7 yrs.	Mean (T1)=19.7 yrs. Mean (T2)=11.3 yrs.	T1=51 T2=61	NR	Mean (T1)=11,310 miles/yr Mean (T2)=12,463 miles/yr	NR	Low
Laberge-Nadeau et al.(75)	2000	type 1/type 2	1,063†	<66 yrs	NR	NR	100	NR	NR	Good
McGwin et al.(76)	1999	type 1/type 2	129	All ≥65 yrs	NR	≈50.0	NR	<4,000 miles/yr: ≈32% 4,000–7,999 miles/yr: ≈24% 8,000–13,000 miles/yr: ≈21% >13,000 miles/yr: ≈23%	74.5%	Low
Gressert et al.(77)	1994	type 1/type 2	121	All age 70	NR	NR	NR	NR	NR	Low
Koepsell et al.(78)	1994	type 1/type 2	88	All ≥65 yrs	NR	50.0	NR	<5000 miles/yr 44% 5,000–10,000 miles/yr: 26% 10,000–15,000 miles/yr: 20% >15,000 miles/yr: 10%	95%	Low
De Klerk et al.(79)	1993	type 1/type 2	8,623	NR	NR	NR	NR	NR	NR	Unclear
Hansotia et al.(80)	1991	type 1/type 2	484	Mean=59.0 yrs	Mean=8.7 yrs	57.2	NR	NR	NR	Unclear
Stevens et al.(42)	1989	type 1/type 2	354	Mean=41 yrs (SD=13)	NR	61.3	NR	<8000 km/yr: 32% 8000–17,700 km/yr: 20% 17701–26000 km/yr: 8% 26001–≥32000 km/yr: 9%	NR	Unclear
Eadington et al.(43)	1988	Type 1 only	187	Mean=52 yrs (Rng=28–81)	Mean=22 yrs (Rng=12–43)	63.9	NR	NR	NR	Unclear

Reference	Year	Type of diabetes	(number of individuals with diabetes included (n=)	Age distribution	Duration of diabetes	% Male	% CMV drivers	Driving exposure	% white	Generalizabiiity to target population
Songer et al.(44)	1988	Type 1 only	158	21–29 yrs: 22% 30–39 yrs: 67% 40–49 yrs: 11%	NR	55.7	NR	Mean=16.4 (SD=5.3) yrs driving Mean=11,824 (SD=12,467) miles/yr	97.5	Low
Davis et al.(81)	1973	type 1/type 2	108	NR	NR	NR	NR	NR	NR	Unclear
Ysander et al.(82)	1970	type 1/type 2	219	18–20 yrs: 2% 21–25 yrs: 4% 26–30 yrs: 3% 31–40 yrs: 15% 41-50 yrs: 21% 51–60 yrs: 30% >60 yrs: 25%	NR	NR	NR	1–4,999 miles/yr: 17% 5,000–9,999 miles/yr: 32% 10,000–19,999 miles/yr: 29% >20,000 miles/yr: 22%	NR	Low
Campbell et al.(83)	1969	type 1/type 2	346	15–19 yrs: 2% 20–24 yrs: 3% 25–34 yrs: 6% 35–44 yrs: 9% 45-54 yrs: 18% 55–64 yrs: 25% >65 yrs: 37%	NR	81.9	NR	NR	NR	Unclear
Crancer et al.(84)	1968	type 1/type 2	7,646	NR	NR	NR	NR	NR	NR	Unclear
Ysander et al.(85)	1966	type 1/type 2	256	NR	NR	NR	NR	NR	NR	Unclear
Waller et al.(86)	1965	type 1/type 2	287	Mean (males)=42.1 yrs Mean (females)=38.1 yrs	NR	74.5	NR	Mean (males)= 12,600 miles/yr Mean (females)= 5,200 miles/yr	NR	Low

Findings

The findings of the 16 studies that addressed Key Question 1 are presented in detail in the study summaries presented in Appendix G. As stated above, only one of these 16 studies included a population of individuals comprised of CMV drivers.(75) Also, the evidence base for Key Question 1 is composed of two distinct types of case-control study. Thirteen case-control studies compared crash risk among individuals with diabetes (cases) and a comparable group of individuals who do not have the disorder (controls). Three case-control studies compared the prevalence of diabetes among individuals who had been involved in a crash (cases) and a comparable group of individuals who had not (controls). Outcome data from the former set of studies were presented as the risk ratio[13]. Outcome data from the latter group of studies were presented as the odds ratio[14].

Although both types of study may be considered to address the same question from a qualitative perspective (does diabetes represent an increased crash risk), they differ significantly from a quantitative perspective. In addition to quantitative differences in the two types of study, it turned out that all three of the studies that compared the prevalence of diabetes among individuals who had been involved in a crash with a comparable group of individuals who had not, enrolled individuals over the age of 65. Consequently, we have analyzed data from the two different study types separately and we place more weight on the findings of our analyses of data extracted from the larger data set from the 13 studies that compared crash risk among individuals with diabetes with a comparable group of individuals who do not have the disorder.

Findings of single case-control study directly generalizable to CMV license holders

One well-designed and -executed (Quality Score=9.4) case-control study presented crash risk data obtained from CMV drivers with diabetes.(75) Laberge-Nadeau et al. performed a study in which diabetic truck-permit holders in Québec, Canada were group matched by age with a random sample of healthy permit holders. Data on permits, medical conditions, and crashes involving 13,453 permit holder–years in 1987–1990 were extracted from the files of the public insurer for automobile injuries in Québec. The investigators obtained additional health status data from the provincial public health insurer and driving pattern and exposure data were obtained by means of a telephone survey.

Data were analyzed using multilevel negative binomial regression models in which each driver's medical status was nested within permit class. Mean yearly crash rates per driver with diabetes were compared with those occurring among drivers in good health using age and both quantitative and qualitative measures of driving exposure as covariates. The resulting risk ratios provided the marginal effect of belonging to the particular group in terms of relative crash risks, all other variables being equal. In some cases exposure data from some CMV drivers could not be obtained. Consequently, Laberge-Nadeau et al. presented the findings of several models. In this evidence report, we focus on their model, which included exposure information (Table 14).

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[13] The risk of crash among individuals with diabetes divided by the risk of crash among comparable individuals who do not have diabetes.

[14] The odds of having diabetes having been involved in a crash divided by the odds of having diabetes if not involved in a crash.

Table 14. Crash RRs and 95% CIs for professional drivers 1987–1990

Explanatory variable	N=	Mean	RR	95% CI
Class AT				
Good health	1,736	0.17	1.00	Reference category
Diabetes without complications	369	0.13	0.81	0.58–1.14
Diabetes with complications	299	0.15	0.87	0.61–1.25
Diabetes treated with insulin	121	0.11	0.65	0.35–1.21
Class ST				
Good health	795	0.14	1.00	Reference category
Diabetes without complications	**127**	**0.24**	**1.76***	**1.06–2.91**
Diabetes with complications	84	0.13	0.96	0.48–1.91
Diabetes treated with insulin	62	0.16	1.02	0.48–2.17
Distance driven (Class AT)				
<20,000 km	935	0.11	1.00	Reference category
20,001–50,000 km	836	0.17	1.55*	1.16–2.08
50,001–100,000 km	447	0.20	1.87*	1.33–2.64
>100,000 km	307	0.21	1.94*	1.26–2.99
Distance driven (Class ST)				
<20,000 km	497	0.13	1.00	Reference category
20,001–50,000 km	380	0.17	1.19	0.79–1.79
>50,000 km	191	0.19	1.40	0.82–2.38

*Statistically significant difference; AT=articulated truck; ST=straight truck

The increased crash risk for professional drivers with a permit to drive a straight truck and with uncomplicated diabetes that is not treated with insulin is surprising. First, the incidence of hypoglycemia is known to be higher among individuals treated with insulin than that among individuals treated with other agents or diet alone. Consequently, one might reasonably expect to see a higher risk ratio among individuals whose diabetes is controlled with insulin than is seen among individuals controlled with oral hypoglycemic agents or diet alone (76% of individuals in this group were taking a sulfonylurea). Second, one might expect that the same patterns of risk observed among drivers of straight trucks would also be observed among drivers of articulated trucks. This was not the case.

One possible reason for the unexpected results might be that employers of drivers of articulated trucks use higher medical standards when hiring drivers. For example, the medical restrictions for diabetic truck drivers are more stringent in some Canadian provinces and for interstate travel in the United States.

While the findings of the study of Laberge-Nadeau et al. are informative, they do not, in and of themselves, provide sufficient evidence to allow an evidence-based conclusion about the relationship between the crash risk among CMV drivers and diabetes to be drawn. Such conclusions require the presence of confirmatory findings from other well-designed studies. As a consequence of the lack of direct evidence from CMV drivers, one must look to other evidence sources that have evaluated crash risk among much broader populations of drivers. An analysis of the results of such studies, while not necessarily directly generalizable to CMV drivers, will at least allow one the opportunity to draw evidence-based conclusions pertaining to the relationship between diabetes and the risk for a motor vehicle crash risk among drivers in general.

Findings of 13 case-control studies that compared risk of crash among comparable drivers with and without diabetes

Thirteen included studies (Quality Score=7.0; Low) reported on the ratio of the incidence of crash experienced by individuals with diabetes and the incidence of crash observed among a comparable group of individuals who did not have the disorder (Table 15). An initial review of the results of the 13 individual studies suggests that the available data on crash risk among individuals with diabetes is inconsistent. Six studies provided evidence that diabetes is a significant risk factor for involvement in a motor vehicle accident,(40,75,80,83,84,86) while the results of the remaining seven studies found no such evidence.(42-44,79,81,82,85)

Although there are apparent differences in the qualitative findings of the included studies, close scrutiny of the risk ratio data from these studies found that their results are in fact quite similar (Figure 5). Formal testing of the data for the presence of heterogeneity (differences in the results of different studies that cannot be explained by chance alone) found that the findings of the 13 studies were homogeneous (I^2=13.9%; Q=18.2, *P*=0.111). In other words, homogeneity testing found that the apparent differences in the findings of the included studies were no greater than those that one might expect to see by chance alone. Such a finding is important because it suggests that the differences in the design, conduct, and enrollees across studies had little impact on outcome.

Because the findings of the 13 included studies were homogeneous, we next pooled their rate-ratio data using an inverse-variance weighted, fixed-effects model meta-analysis. The aim of this analysis was to determine a single weighted average estimate of the risk ratio from the pooled results of the individual studies. Pooling of these data yielded a summary risk ratio of 1.19 (95% CI: 1.08–1.31, *P*=0.0004). In other words, the average driver with diabetes is 1.19 times more likely to be involved in a motor vehicle crash than a comparable driver who does not have diabetes.

In order to test the robustness of this finding, we performed a series of analyses that tested many of the assumptions underlying our original analysis. These analyses, the results of which are presented in Appendix H (Figure H-2 through Figure H-6), included the repetition of the primary meta-analysis using a random-effects model, several fixed-effects cumulative meta-analyses, and a test of publication bias. None of our sensitivity analyses overturned the findings of our primary analysis. Consequently, we believe the findings of our analysis to be robust.

Having determined that drivers with diabetes are at an elevated risk for a motor vehicle crash, we next attempted to determine whether there were any specific subgroups of drivers with diabetes who were at a particularly high risk for crash. In particular, we were interested in determining whether drivers with diabetes that was controlled using insulin were at a higher risk than individuals treated using either pharmacotherapy or diet alone. Because very few included studies reported on how the individuals with type 2 diabetes that they enrolled controlled their diabetes (some of whom would require insulin), such a comparative analysis was not possible. However, five of the 13 included studies did provide separate crash risk data solely for drivers who were insulin treated.(40,42-44,75) Consequently, it was possible to attempt to determine an estimate of the risk ratio associated with this subpopulation of drivers.

Included among the five studies cited above was the study of Laberge-Nadeau et al.(75) As discussed earlier, this study is the only included study that specifically assessed crash risk among CMV drivers with diabetes. Laberge-Nadeau and colleagues presented data separately for articulated and straight truck drivers. Making an assumption that the latter two data sets can be considered independent from one another (although sampled from the same database, the two groups consist of a different set of cases and controls), we treated them as if they were two separate studies. Consequently, a total of six data sets containing information on crash risk among drivers with insulin-dependent diabetes were available for analysis.

Relevant outcome data from these six data sets discussed above are plotted in Figure 6. These data were found to be heterogeneous (I^2=68.97%; Q=16.11, *P*=0.0065). That is, the findings of the six studies differed by more than one would expect by chance alone. Data from a heterogeneous data set cannot be combined in a fixed-effects meta-analysis because they violate the model's underlying assumption of homogeneity. Consequently, we did not calculate a fixed-effects summary estimate of the risk ratio for this data set.

Because data from only six data sets was available to us, we did not attempt to explore the observed heterogeneity using meta-regression techniques. This is the consequence of the fact that, for statistical reasons, we require a minimum of 10 studies before we will attempt such an analysis. Instead, we pooled the available risk-ratio data using random-effects meta-analysis. Random effects meta-analysis allows one to combine heterogeneous data by partitioning the estimated between studies variance component and adding it to the within studies variance of each included study.(3,61) The result of this meta-analysis, which is presented in Figure 7, was inconclusive. Given the findings of the previous analysis on the risk of a motor vehicle crash that is associated with diabetes in general, the findings of this analysis do not provide support for the contention that the risk for a motor vehicle crash is particularly high among individuals with diabetes that require treatment with insulin (RR=1.11; 95% CI: 0.80–1.80, *P*=0.676).

The primary risk factor for a crash among individuals with diabetes was traditionally thought to be hypoglycemia. As there is a reasonably large body of literature showing that hypoglycemia occurs more often among individuals treated with insulin than among those treated by pharmacotherapy or diet alone, the result above is contrary to expectations. One might reasonably expect to observe that individuals with insulin-treated diabetes are at a particularly high risk for a motor vehicle crash when compared with individuals who control their diabetes by other means.

One possible explanation for the finding that drivers with insulin-treated diabetes do not appear to be at a particularly high risk for a motor vehicle crash has already been mentioned. Laberge-Nadeau et al.(75) suggested that a process of self-selection occurs among individuals with insulin-treated diabetes and that the most severely affected individuals either restrict their driving or do not drive at all. As a consequence, crash-risk estimates determined for drivers with insulin-dependent diabetes are based on a subset of individuals with lower rates of hypoglycemia than would be seen if all individuals with insulin-treated diabetes drove. If this is true, indirect estimates of crash risk derived from published incidence rates for severe hypoglycemia that have not been weighted according to driving exposure (we are not aware of any such studies) will tend to overestimate the true crash rate for this group of individuals.

Table 15. Crash Risk in Drivers with Diabetes compared to Drivers without Diabetes

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure adjusted?	Effect Size* (95% CI)	*P*=*	Evidence of increased Crash Risk	*Conclusion*
Cox et al.(40)	2003	Diabetes (Type 1)	% of drivers experiencing event in previous 2 years	19.00	No	RR=2.38 (1.41–3.78)	<0.001	Yes	Evidence that those drivers with both type I and type II diabetes are at increased risk for a motor vehicle accident
		Diabetes (Type 2)		12.00	No	RR=1.5 (0.88–2.56)	0.135	No	
		Control		8.00	No				
Laberge-Nadeau et al.(75)	2000	Diabetes (all drivers)	Events per driver per year.	0.16	Yes	RR=1.07 (0.88–1.30)	0.4976	No	No evidence that drivers with diabetes who drive commercial vehicles in Canada are at increased crash risk
		Control (all drivers)		0.15					
		Diabetes (AT-no comps)	Events per driver per year.	0.13	Yes	RR=0.81 (0.58–1.14)	NS	No	No evidence that drivers with diabetes who drive articulated vehicles in Canada are at increased crash risk.
		Diabetes (AT- comps)		0.15	Yes	RR=0.87 (0.61–1.25)	NS	No	
		Diabetes (AT-Insulin)		0.11	Yes	RR=0.65 (0.35–1.21)	NS	No	
		AT-Control		0.17					
Laberge-Nadeau et al.(75)	2000	Diabetes (ST-no comps)	Events per driver per year.	0.24	Yes	RR=1.76 (1.06–2.91)	<0.05	Yes	Evidence that drivers with diabetes who are not taking medication and drive straight trucks in Canada are at increased crash risk.
		Diabetes (ST- comps)		0.13	Yes	RR=0.96 (0.48–1.91)	NS	No	No evidence that drivers with diabetes controlled with insulin or oral hypoglycemics are at increased crash risk.
		Diabetes (ST-Insulin)		0.16	Yes	RR=1.02 (0.48–2.17)	NS	No	
		ST-Control		0.14					
De Klerk et al.(79)	1983	Diabetes (all)	Events occurring over eight years	27.00	No	RR=1.52 (0.84–2.77)	0.1729	Unclear	No evidence that drivers with diabetes are at increased risk crash risk
		Control		17.80					
Hansotia et al.(80)	1991	Diabetes (all)	Event rate per 1000 person years	68.91	No	RR=1.32 (1.06–1.63)	0.0097	Yes	Evidence that drivers with diabetes are at increased risk crash risk
		Control		52.02					
Stevens et al.(42)	1989	Diabetes (Insulin dependent)	Events occurring over five years	82.00	No	RD=0.93 (0.66–1.32))	0.6783	No	No evidence that drivers with diabetes are at increased risk crash risk
		Control		75.00					
Eadington et al.(43)	1988	Diabetes (Insulin dependent)	Events per 1,000,000 miles	5.40	Yes	RR=0.54 (0.20–1.58)	0.2732	No	No evidence that drivers with type-I diabetes are at increased risk crash risk
		Control		10.00					

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure adjusted?	Effect Size* (95% CI)	*P*=*	Evidence of increased Crash Risk	*Conclusion*
Songer et al.(44)	1988	Diabetes (Insulin dependent)	Events per 100 drivers per 1,000,000 miles	10.40	Yes	RR=2.66 (0.80–7.67)	0.19	No	No evidence that drivers with type-I diabetes are at increased risk crash risk
		Control		3.91					
Davis et al.(81)	1973	Diabetes (all)	Events per 100 drivers per year	7.40	No	RR=1.04 (0.37–2.91)	0.9470	No	No evidence that drivers with diabetes are at increased risk crash risk
		Control		7.10					
Ysander et al.(82)	1970	Diabetes (all)	% of drivers experiencing event during a mean period of 4.7 yrs	3.70	No	0.58 (0.25–1.40)	0.4279	No	No evidence that drivers with diabetes are at increased risk crash risk
		Control		6.40					
Campbell et al.(83)	1969	Diabetes (all)	Total events per 5.5 yrs	91.00	No	RR=1.72 (1.18–1.40)	0.0043	Yes	Evidence that drivers with diabetes are at increased risk crash risk
		Control		53.00					
Crancer et al.(84)	1968	Diabetes (all)	Events per 100 drivers over 6.75 yr period	31.50	No	RR=1.19 (1.01–1.39)	0.0376	Yes	Evidence that drivers with diabetes are at increased risk crash risk
		Control		26.50					
Ysander et al.(85)	1966	Diabetes (all)	% of drivers experiencing event during a mean period of 4.7 yrs	5.00	No	RR=0.65 (0.17–3.38)	0.5290	Unclear	Point estimate only presented. No confidence intervals reported. No P-value reported. Not enough information reported to allow calculation of confidence intervals
		Control		7.70					
Waller et al.(86)	1965	Diabetes (all)	Events per driver per 1,000,000 miles	15.50	No	RR=1.78 (0.76–4.15)	<0.001	Yes	Evidence that drivers with diabetes are at increased risk crash risk.
		Control		8.70					

*Calculated by ECRI. Effect size estimates >1.0 indicate that diabetics are at increased risk for a motor vehicle accident than comparison group; †Authors presented findings of six separate models. The coefficients associated with these models are presented in Appendix E in the study summary tables for Dionne et al; ‡Authors argue that it was not necessary (found no evidence that exposure had an impact on crash rate); §Based on population data from Department of Transportation. CI=Confidence Interval; NC=Not Calculated; NR=Not Reported; NS=Not Statistically Significant; OR=Odds Ratio, RD=Rate Difference; RR=Risk ratio

Figure 5. Crash Risk in Drivers with Diabetes compared to Drivers without Diabetes

Study	LnRR	Var (LnRR)	SD (LnRR)	Lower 95% CL	Upper 95% CL	*P*=
Cox	0.67	0.21	0.46	-0.22	1.57	0.141042
Laberge-Nadeau	0.07	0.01	0.10	-0.13	0.26	0.497553
De Klerk	0.42	0.09	0.30	-0.17	1.01	0.166425
Hansotia	0.28	0.01	0.11	0.06	0.50	0.013115
Stevens	-0.07	0.03	0.17	-0.42	0.27	0.678320
Eadington	-0.62	0.26	0.51	-1.61	0.38	0.224012
Songer	0.98	0.38	0.61	-0.22	2.18	0.110494
Davis	0.04	0.28	0.53	-0.99	1.07	0.940706
Ysander (1970)	-0.54	0.18	0.43	-1.39	0.30	0.204561
Campbell	0.54	0.04	0.19	0.17	0.92	0.004788
Crancer	0.17	0.01	0.08	0.01	0.34	0.037625
Ysander (1966)	-0.43	0.47	0.68	-1.77	0.91	0.528990
Waller	0.58	0.19	0.43	-0.27	1.43	0.184191
Fixed Effects Summary Effect Size			**0.17**	**0.08**	**0.27**	**0.000348**
Heterogeneity tests			Q=	18.16	df=12	P=0.111
			I^2=	33.9%		

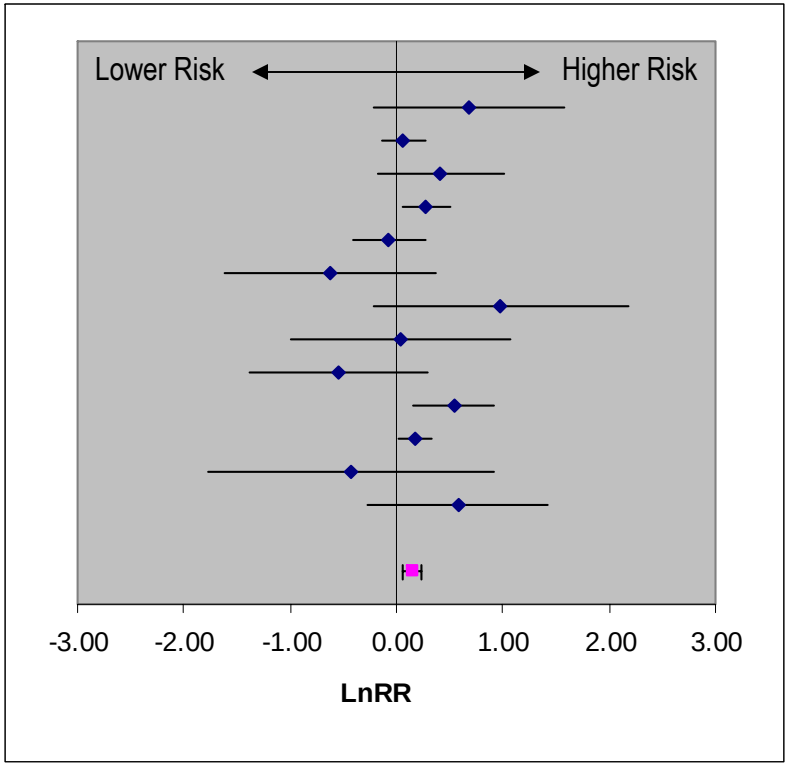


Figure 6. Results of Fixed-Effects Meta-Analysis (Insulin-Treated Diabetes Cohorts)

Study	LnOR	Var	SD	Lower 95% CL	Upper 95% CL	*P*=
Cox	0.87	0.07	0.27	0.34	1.39	0.0012
Laberge-Nadeau (AT)	-0.43	0.10	0.32	-1.05	0.19	0.1726
Laberge-Nadeau (ST)	0.02	0.18	0.43	-0.82	0.86	0.9632
Stevens	-0.07	0.03	0.17	-0.42	0.27	0.6783
Eadington	-0.62	0.26	0.51	-1.61	0.38	0.2240
Songer	0.98	0.38	0.61	-0.22	2.18	0.1105
Fixed Effects Summary Effect Size (LnRR)=			**NC (data heterogeneous)**			
Homogeneity test results:			**I^2=68.97**	**Q=16.11**	**df=5**	***P*=0.0065**

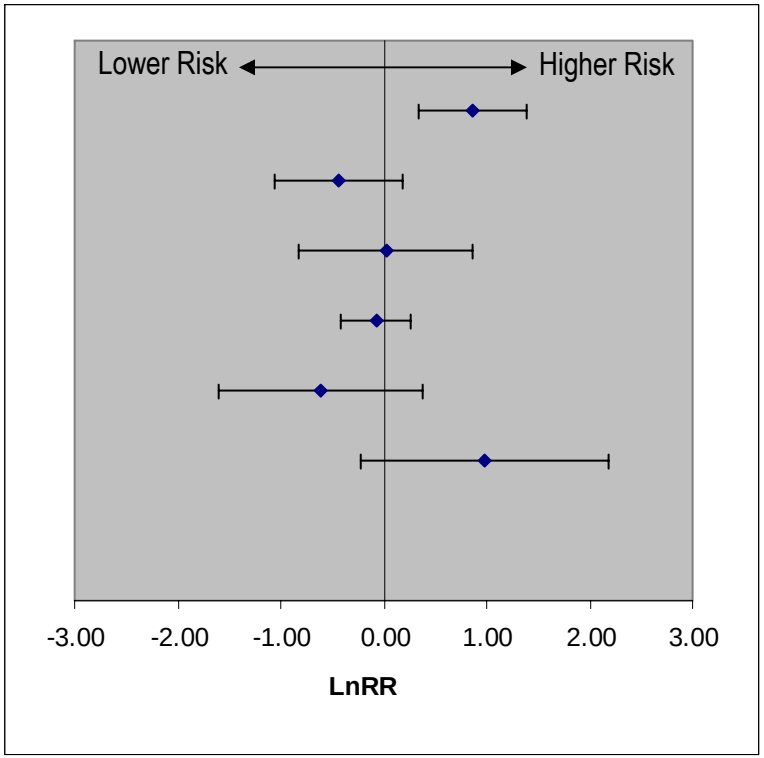
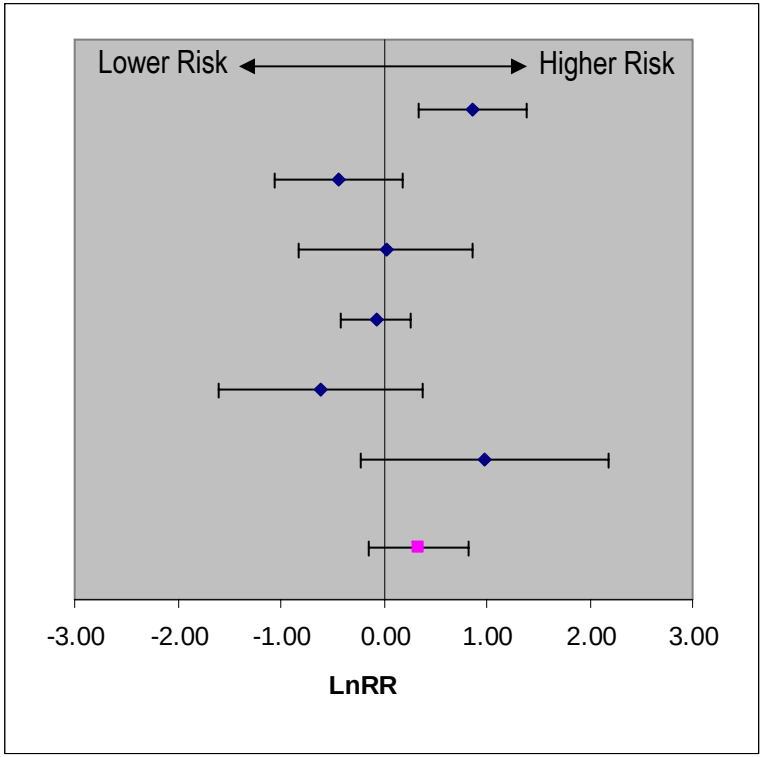


Figure 7. Results of Random-Effects Meta-Analysis (Insulin-Treated Diabetes Cohorts)

Study	LnOR	Var	SD	Lower 95% CL	Upper 95% CL	*P*=
Cox	0.87	0.07	0.27	0.34	1.39	0.0012
Laberge-Nadeau (AT)	-0.43	0.10	0.32	-1.05	0.19	0.1726
Laberge-Nadeau (ST)	0.02	0.18	0.43	-0.82	0.86	0.9632
Stevens	-0.07	0.03	0.17	-0.42	0.27	0.6783
Eadington	-0.62	0.26	0.51	-1.61	0.38	0.2240
Songer	0.98	0.38	0.61	-0.22	2.18	0.1105
Random Effects Summary Effect Size (LnRR=)			**1.11 (0.68–1.80)**			***P*=0.676**



Findings of case-control studies that compared prevalence of diabetes among drivers who did and did not crash

Three included studies reported on the ratio of the odds of a driver having diabetes and being involved in a motor vehicle crash and the odds of having diabetes and not being involved in a motor vehicle crash.(76-78) All three studies focused on crash risk among individuals who were over the age of 65. Because the generalizability of the findings of these studies to CMV drivers is likely to be limited, we consider the set of analyses that follow as secondary to the primary analysis presented in the previous section. We include this set of analyses in the main body of the evidence report because although they may be of limited generalizability, the studies do offer the potential for gaining insight into the relative influence of different treatment regimens on crash risk.

In addition to reporting on relevant outcome crash data for all individuals with diabetes (regardless of how it was controlled), each of the three studies included in the present set of analyses also reported on the odds ratio for several important subgroups that were classified by how diabetes was controlled; individuals who required insulin (all three studies), individuals who required pharmacotherapy (two studies),(76,78) and individuals who maintained adequate glycemic control through a controlled diet alone (two studies).(76,78) Relevant outcome data extracted from these three studies are presented in Table 16.

Findings of analysis of data from all individuals with diabetes

As stated above, all three included studies reported relevant crash risk data for individuals with diabetes regardless of how it was controlled. One included study found that individuals with diabetes are at increased risk for a motor vehicle accident.(78) The remaining two studies, however, did not make such an observation.(76,77) Homogeneity testing found that the differences in the findings of the three studies were greater than what one might expect by chance alone (I^2=72.98%; Q=7.69, *P*=0.0214). Consequently, we did not pool data using a fixed-effects model meta-analysis. Because relevant data from only three studies are available at this time, we did not attempt to explore the observed heterogeneity using meta-regression.

Pooling of these data using random-effects meta-analysis (Figure 8) found that drivers with diabetes tend to be overrepresented among samples of drivers who have experienced a crash (Odds Ratio=1.32, 95% CI: 0.63–1.90; *P*=0.1760). Because the confidence intervals encompass an odds ratio of 1, however, we cannot discern whether this tendency in the data is meaningful; our findings are thus inconclusive.

Findings of analysis of data from individuals with diabetes controlled using insulin

All three studies included in the previous analysis presented data for a subgroup of enrollees who used insulin to control their diabetes. As was the case above, one of the three studies found that individuals with diabetes controlled using insulin were at an increased risk for hypoglycemia.(78) However, the remaining two studies did not provide evidence of such a difference. Despite the apparent qualitative differences in the findings of the three studies, homogeneity testing found that the results of these three studies were quantitatively homogeneous (I^2=44.46; Q=3.6, df=2, P=0.1695). Consequently, we pooled the available

data using a fixed-effects meta-analysis (Figure 9). Pooling of these data found that drivers with diabetes controlled using insulin tend to be overrepresented among samples of drivers who have experienced a crash (Odds Ratio=1.35; 95% CI: 0.86–1.70, P=0.1695). Because the confidence intervals encompass an odds ratio of 1, we cannot discern whether this tendency in the data is meaningful; our findings are inconclusive.

Findings of analysis of data from individuals with diabetes controlled using pharmacotherapy or diet alone

Two of the three included studies presented data for separate subgroups of enrollees who were controlled either by pharmacotherapy or by diet alone. Because data from only two studies were available, we did not pool these data to obtain a summary estimate of the odds ratio for either subgroup. Although there was a tendency in the data to suggest that drivers who control their diabetes with oral agents may be overrepresented and drivers with diabetes controlled by diet alone may be underrepresented (Figure 10), in no case did the 95% confidence intervals exclude an odds ratio of 1 (logOR of 0). Consequently, we cannot discern whether any of the tendencies that we have we observed in the data are meaningful.

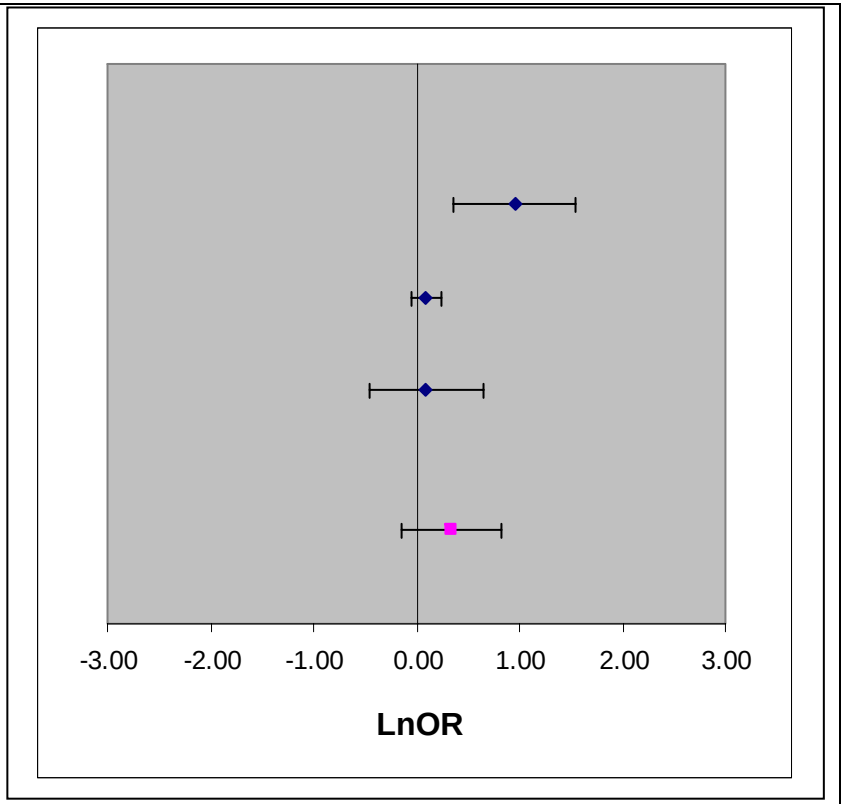
Table 16. Findings of Case-Control Studies that Compared Prevalence of Diabetes in Crash and Non-Crash Cohorts

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted?	Effect Size* (95% CI)	*P*=*	Evidence of Increased Crash Risk	*Conclusion*
McGwin et al.(76)	1999	Diabetes (all)	Difference in prevalence of diabetes in at fault crash and non-crash cohorts	NR	Yes	OR=1.1 (0.7–1.9)	0.7325	No	No evidence that individuals with diabetes at increased crash risk.
		Control (all)		NR					
		Diabetes (diet control)		NR	Yes	OR=0.6 (0.2–2.5)	0.5216	No	
		Control (diet control)		NR					
		Diabetes (Pharmacologic)		NR	Yes	OR=1.3 (0.7–2.2)	0.3283	No	
		Control (Pharmacologic)		NR					
		Diabetes (insulin)		NR	Yes	OR=1.3 (0.6–2.9)	0.4410	No	
Gressert et al.(77)	1994	Diabetes (all)	Difference in prevalence of diabetes in crash and non-crash cohorts	NR	No	OR=1.01 (0.80–1.27)	0.1936	No	No evidence that individuals with diabetes at increased crash risk.
		Control (all)		NR					
		Diabetes (ins. dependent)		NR	No	OR=1.13 (0.63–2.04)	0.6851	No	
		Control (ins. dependent)		NR					
		Diabetes (non-ins. dep.)		NR	No	OR=0.99 (0.77–1.27)	0.9370	No	
		Control (non-ins. dep.)		NR					
Koepsell et al.(78)	1994	Diabetes (all)	Difference in prevalence of diabetes in at fault crash and non-crash cohorts	NR	No	OR=2.6 (1.4–4.7)	0.0016	Yes	Evidence that individuals with diabetes t increased crash risk.
		Control (all)		NR					
		Diabetes (insulin)		NR	No	OR=5.8 (1.2–28.7)	0.0312	Yes	Evidence that individuals with diabetes controlled with insulin at increased crash risk.
		Control (insulin)		NR					
		Diabetes (oral hypoglycemics)		NR	No	OR=3.1 (0.9–11.0)	0.0800	No	Unclear whether individuals with oral hypoglycemics controlled diabetes at increased crash risk.
		Control (oral hypoglycemics)		NR					
		Diabetes (diet alone)		NR	No	OR=0.9 (0.4–2.4)	0.8332	No	No evidence that individuals with diet controlled at increased crash risk.
		Control (diet alone)		NR					

NR=not reported; OR=odds ratio

Figure 8. Results of Meta-Analysis of Log Odds Ratio Data (Overall)

Study	LnOR	Var	SD	Lower 95% CL	Upper 95% CL	*P*=
Koepsell	0.96	0.09	0.30	0.36	1.55	0.0016
Gressert	0.10	0.01	0.07	-0.05	0.24	0.1936
McGwin	0.10	0.08	0.28	-0.45	0.64	0.7325
Random effects Summary Effect Size			NC	**NC**	**NC**	**NC**
Homogeneity tests			**I^2=73.98**	**Df=2**	**Q=7.69**	***P*=0.0214**
Random effects Summary Effect Size			**0.34**	**-0.15**	**0.83**	**0.1760**



This analysis does not provide evidence that the odds of experiencing a crash are increased among individuals with diabetes

Figure 9. Results of Fixed Meta-Analysis of Odds-Ratio Data (Individuals using Insulin)

Study	LnOR	Var	SD	Lower 95% CL	Upper 95% CL	*P*=
Koepsell	0.26	0.17	0.41	-0.54	1.06	0.5216
Gressert	0.12	0.09	0.30	-0.47	0.71	0.6851
McGwin	1.76	0.67	0.82	0.16	3.36	0.0312
Fixed Effects Summary Effect Size			0.30	**-0.15**	**0.53**	**0.0192**
Homogeneity tests			**I^2=44.46**	**Df=2**	**Q=3.6**	***P*=0.1695**

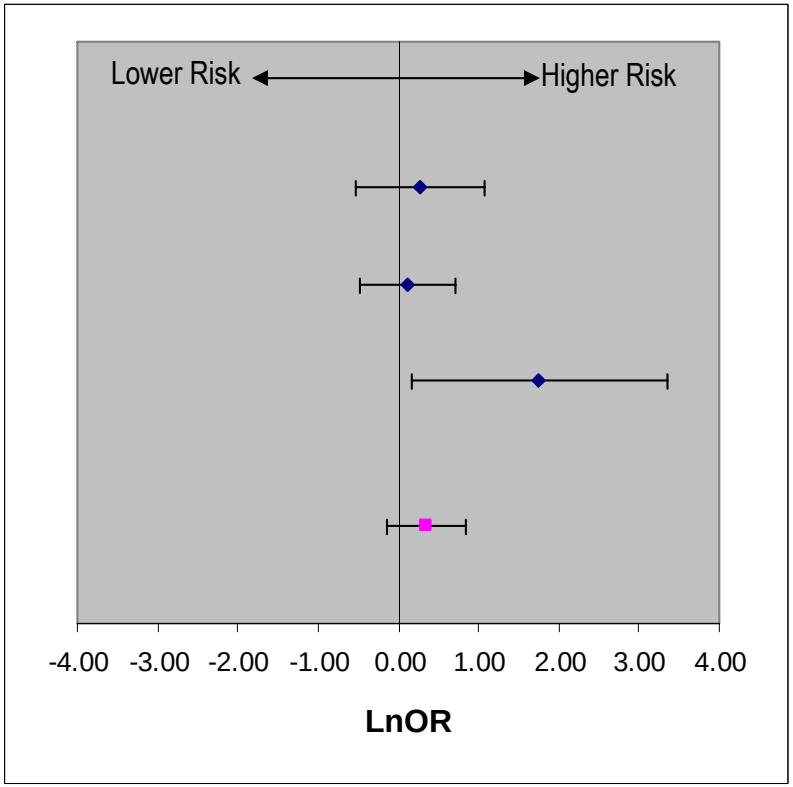
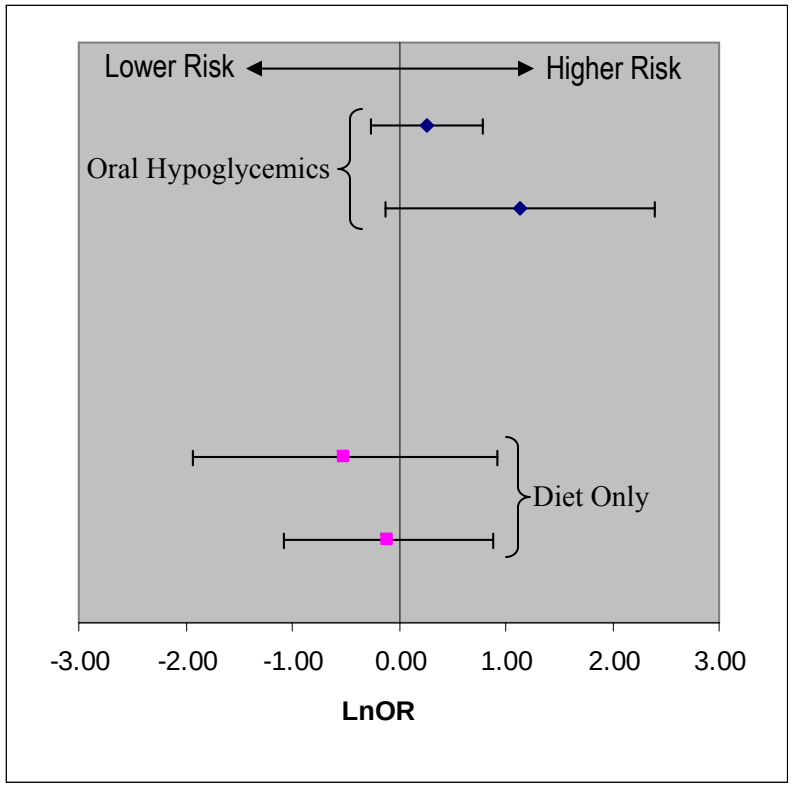


Figure 10. Log Odds Ratio in Drivers who Control Diabetes with Oral Agents or Diet Alone

Study	LnOR	Var	SD	Lower 95% CL	Upper 95% CL	*P*=
McGwin	0.26	0.07	0.27	-0.26	0.79	0.3283
Koepsell	1.13	0.42	0.65	-0.14	2.40	0.0800
McGwin	-0.51	0.53	0.73	-1.94	0.92	0.4829
Koepsell	-0.11	0.25	0.50	-1.09	0.88	0.8332



Section Summary

A number of conclusions can be drawn from the findings of the analyses described above. These conclusions are presented below:

1. **A paucity of data from studies that enrolled CMV drivers with diabetes precludes one from determining whether CMV drivers with diabetes are at increased risk for a motor vehicle accident.**

   A single, moderate quality case-control study evaluated crash risk among CMV drivers with diabetes as compared with comparable CMV drivers who did not have the disorder.(75) This study was the only included study that specifically assessed crash risk among CMV drivers with diabetes. While the results of this Canadian study are directly applicable to CMV drivers in the United States, it is not a high-quality study and its findings have not been replicated. Consequently, one cannot draw an evidence-based conclusion pertaining to the whether CMV drivers with diabetes are at an increased risk for a motor vehicle accident.

2. **As a group, drivers with diabetes are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Weak).**

   - **The magnitude of this increased risk is small but statistically significant (Risk Ratio=1.19; 95% CI: 1.08–1.31). In other words, the crash risk for an individual with diabetes is 1.19 times greater than a comparable individual who does not have the condition (Stability of Estimate of Risk Ratio: Weak).**

   Thirteen case-control studies (Overall Quality=Low) compared crash risk among drivers with diabetes (cases) and a comparable group of drivers who do not have the disorder (controls).[15] *Outcome data from this evidence base were presented in terms of a risk ratio. This is the ratio of the incidence of crash among drivers with diabetes (cases) and the incidence of crash among comparable drivers who do not have the disorder. Risk Ratio values above 1 indicate that drivers with diabetes are at a higher risk for crash than drivers who do not have the disorder.*

   Quantitative analysis of outcome data from the 13 included studies found that the outcome data was homogeneous. A fixed effects meta-analysis in which these data were pooled found that the risk for crash among drivers with diabetes was 1.19 (95% CI: 1.08–1.31) times greater that the risk for crash among drivers who do not have the disorder. A series of sensitivity analyses designed to test the stability of this estimate found this estimate to be robust.

   Despite the robustness of our findings we have refrained from drawing strong conclusions. This is because case-control studies are inherently susceptible to bias. Also, many of the studies included in the analysis were either poorly designed and/or conducted, or they were poorly reported. The most important potential source of bias

[15] Though the literature is reasonably consistent in labeling this study design as a case-control study, some argue that this study design is better described as a retrospective cohort study. It is argued that individuals are allocated to comparison group by virtue of an exposure (in this case exposure to the disease diabetes) and not by outcome (in this case crash status).

to affect some of the studies in this evidence base was the failure to control for differences in exposure to risk (the amount of time driving) among the cases and controls. Having said this, the fact that data extracted from the 13 studies was homogeneous suggests that failure to control for differences in exposure did not result in biased risk-ratio estimates. Also, a sensitivity analysis in which risk-ratio data were compared between two subgroups of studies (one subgroup composed of studies that controlled for exposure and the second subgroups consisting of studies that did not) found no evidence that failure to control for exposure resulted in a systematic over-r or underestimate of the observed risk ratio.

3. **Whether drivers with type 1 or type 2 diabetes are overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.**

   Three case-control studies (Overall Quality=Moderate), all of which enrolled individuals over the age of 65, compared the prevalence of drivers with diabetes among a cohort of drivers who had experienced a crash (cases) with the prevalence of drivers with diabetes among a cohort of drivers who had not experienced a crash (controls). Outcome data from this evidence base were presented as odds ratios. An odds ratio is the ratio of the odds of having diabetes and having been in a crash and the odds having diabetes and having not been in a crash. Values above 1 indicate that drivers with diabetes are at a higher risk for crash than non-diabetics (the odds of having diabetes in the crash group is higher than the odds of having diabetes in the non-crash group.

   Homogeneity testing found that the findings of the three included studies differed significantly. Because of the small size of the evidence base, we did not attempt to explain the inconsistency in the findings of the three studies. Since the findings of these three studies cannot be described by a single odds ratio value (the presence of heterogeneity precludes this), we do not present a single estimate of the odds ratio. Instead, we pooled the data using random effects meta-analysis. Random effects meta-analysis allows one to pool heterogeneous data by incorporating the observed between-studies variance into calculation of the summary effect size estimate and its confidence intervals. While this does not allow one to draw evidence-based conclusions about the magnitude of effect, it does allow one to draw conclusions about the direction of effect.

   As would be expected from the findings of the previous analysis, the results of the present analysis found that drivers with diabetes do tend to be overrepresented among samples of drivers who have experienced a crash. However, this overrepresentation is not statistically significant (Odds Ratio=1.41; 95% CI: 0.86–2.29, P=0.1760). Consequently, we must conclude that at the present time, it remains unclear whether drivers with diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. More data are required before an evidence-based conclusion about whether drivers with diabetes are overrepresented among populations of drivers who have crashed.

4. **Whether the subgroup of drivers with diabetes that is controlled by insulin is overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.**

   All three of the case-control studies included in the previous analysis also attempted to determine whether drivers with diabetes treated using insulin are overrepresented among populations of drivers who have experienced a motor vehicle crash. These data were found to be homogeneous. Consequently, they were pooled using fixed-effects meta-analysis. As was the case in the previous analysis, the present analysis found that drivers with diabetes controlled using insulin tend to be overrepresented among samples of drivers who have experienced a crash. However, this overrepresentation is not statistically significant (Odds Ratio=1.35; 95% CI: 0.86–1.70, P=0.1695). Consequently, we conclude that at the present time, it remains unclear whether drivers with diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. More data are required before an evidence-based conclusion about whether drivers with diabetes controlled by insulin are overrepresented among populations of drivers who have crashed.

Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among drivers with diabetes mellitus?

As stated in the *Background* section of this report, hypoglycemia is common among drivers who are receiving insulin or pharmacotherapy aimed at reducing blood glucose to near normal levels (see Table 3). Evidence suggests that hypoglycemia occurs more often in insulin-dependent diabetes than in diabetes that can be controlled through pharmacotherapy. Anecdotal evidence suggests that at least some accidents experienced by drivers with diabetes can be attributed to a hypoglycemic episode (see Table 4). Consequently, one would expect drivers with diabetes to be at an increased risk for a motor vehicle crash. Indeed our analysis of crash risk data extracted from 17 epidemiological studies (see Key Question 1) found that as a group, drivers with diabetes are at a slightly increased risk for a motor vehicle accident when compared with drivers who do not have the disorder. Though the latter finding might be construed as providing proof that hypoglycemia represents an important risk factor for crash involvement, the evidence linking hypoglycemia to increased crash risk is, in fact, far from convincing.

As part of our evaluation of the evidence that addressed Key Question 1, we attempted to determine whether crash risk is higher among drivers who depend on insulin to control their blood glucose levels. The rationale for this analysis was that drivers who are insulin dependent are known to experience a higher incidence of hypoglycemia than drivers who control their diabetes using pharmacotherapy or by diet alone. Consequently, if hypoglycemia were the primary cause of the excess crash risk observed among drivers with diabetes, one would logically expect to observe higher crash rates among drivers with insulin dependent diabetes. Our analyses failed to provide compelling evidence that such drivers were at a higher risk for a motor vehicle crash.

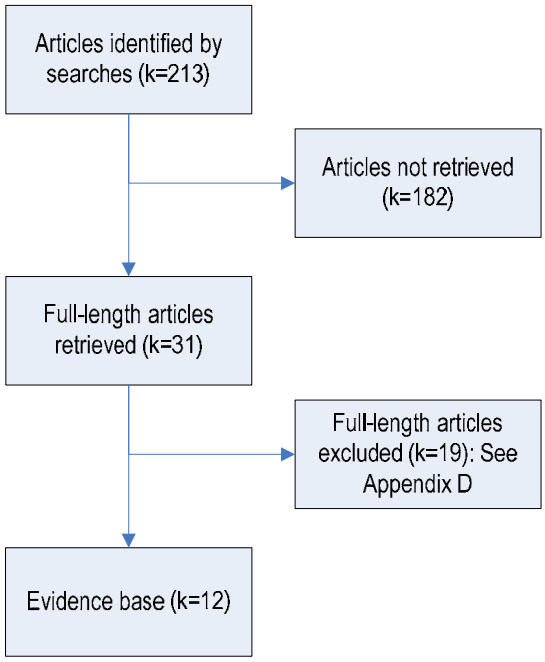
The purpose of Key Question 2, then, is to evaluate data from driving simulation studies and driving-related cognitive and psychomotor function studies to determine whether

hypoglycemia is likely to be an important contributor to the excess crash risk observed among drivers with diabetes.

Identification of Evidence Base

The identification of the evidence base for Key Question 2 is summarized in Figure 14. Our searches[16] identified a total of 213 articles that appeared to be relevant to this key question. Following application of the retrieval criteria[17] for this question, 31 full-length articles were retrieved and read in full. Of these 31 retrieved articles, 12 articles were found to meet the inclusion criteria[18] for Key Question 2. Table D-2 of Appendix D lists the 19 articles that were retrieved but then excluded and provides the reason for their exclusion. Table 17 lists the 12 articles that met the inclusion criteria for Key Question 2.

Figure 11. Development of Evidence Base for Key Question 2



[16] See Appendix A for search strategies
[17] See Appendix B for retrieval criteria
[18] See Appendix C for inclusion criteria

Table 17. Evidence Base for Key Question 2

Reference	Year	Part of Key Question Addressed	Study Location	Country
Cox et al.(88,89)	2000	Part a	University of Virginia Health System, Charlottesville, Virginia	USA
Lobmann et al.(90)	2000	Part b	Magdeburg University Medical School, Magdeburg	Germany
Weinger et al.(91)	1999	Part b	Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts	USA
Dreisen et al.(92)	1995	Part b	University of Virginia Health System, Charlottesville, Virginia	USA
Cox et al.(93)	1993	Part a	University of Virginia Health System, Charlottesville, Virginia	USA
Blackman et al.(94)	1992	Part b	University of Chicago, Illinois	USA
Lingenfelser et al.(95)	1992	Part b	Eberhard-Karls University, Tübingen	Germany
Hoffman et al.(96)	1989	Part b	University of Kansas School of Medicine, Wichita, Kansas	USA
Heller et al.(97)	1987	Part b	Nottingham University Medical School, Nottingham	UK
Holmes et al.(98)	1986	Part b	University of Iowa, Iowa City, Iowa	USA
Herold et al.(99)	1985	Part b	University of Chicago, Illinois	USA
Holmes et al.(100)	1983	Part b	University of Iowa, Iowa City, Iowa	USA

Evidence Base

This subsection provides a brief description of the key attributes of the 12 studies that met the inclusion criteria for this key question. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles. Detailed information pertinent to this section that has been extracted from included studies is presented in the *Study Summary Tables* that can be found in Appendix G.

The primary characteristics of the 12 included studies that address Key Question 2 are presented in Table 18. All 12 studies were prospective. Some compared the response to induced hypoglycemia among drivers with diabetes to drivers without the disease. For the purposes of this evidence report, however, such a comparison is superfluous. We are concerned only with the effects of hypoglycemia on simulated driving ability and cognitive or psychomotor function among individuals with diabetes. Consequently, we focus our attention on changes in driving ability or cognitive/psychomotor function that may occur among individuals with diabetes during controlled and differing levels of hypoglycemia when compared with euglycemic conditions. From this standpoint, all included trials are considered to be single arm before–after studies in which samples of drivers with diabetes were assessed under euglycemic conditions and then again at various controlled levels of induced hypoglycemia.

Table 18. Key Study Design Characteristics of Studies that Address Key Question 2

Reference	Year	Study Design	Type of diabetes	N=	Range of conditions tested	Relevant outcomes assessed
Simulated driving studies						
Cox et al.(88)	2000	Prospective single arm multiple condition* (participants act as own controls)	Type 1	37	Euglycemia (6.7 mmol/L) Hypoglycemia (2.2 mmol/L)†	Steering Braking Speed control
Cox et al.(93)	1993	Prospective single arm multiple condition* (participants act as own controls)	Type 1	25	Euglycemia (6.4 mmol/L) Hypoglycemia (2.4 mmol/L)†	Steering Speed control
Hoffman et al.(96)*	1989	Prospective single arm multiple condition (participants act as own controls)	Type 1	18	Euglycemia (5.6 mmol/L) Hypoglycemia (2.8 mmol/L)	Steering Speed control
Cognitive and psychomotor function studies						
Lobmann et al.(90)	2000	Prospective single arm multiple condition* (participants act as own controls)	Type 1	12	Euglycemia (6.1 mmol/L) Hypoglycemia (2.6 mmol/L)†	Selective attention task (custom)
Weinger et al.(91)	1999	Prospective single arm multiple condition (participants act as own controls)	Type 1	60	Euglycemia (6.7 mmol/L) Hypoglycemia (2.2 mmol/L)†	Reaction Time (MCRTA) Attention (DVT) Selective attention, mental flexibility, visual spatial skills (TMT A and B)
Dreisen et al.(92)	1995	Prospective single arm multiple condition (participants act as own controls)	IDDM	25	Euglycemia (NR) Hypoglycemia (2.5 mmol/L)†	Reaction time (NES2)
Blackman et al.(94)	1992	Prospective single arm multiple condition* (participants act as own controls)	IDDM	10	Euglycemia (5.6 to 4.4 mmol/L) Hypoglycemia (2.5 mmol/L)†	Reaction Time
Lingenfelser et al.(95)	1992	Prospective single arm multiple condition (participants act as own controls)	IDDM	10	Euglycemia (5.5 mmol/L) Hypoglycemia (2.2 mmol/L)†	Selected cognitive and psychomotor skills (PSE-Syndrome-Test) Reaction Time (VRT)
Hoffman et al.(96)	1989	Prospective single arm multiple condition (participants act as own controls)	Type 1	18	Euglycemia (5.6 mmol/L) Hypoglycemia (2.8 mmol/L)	Reaction time (visually cued reaction timer) Vigilance and motor control (pursuit rotor) Selective attention, mental flexibility, visual spatial skills (TMT A and B)
Heller et al.(97)	1987	Prospective single arm multiple condition (participants act as own controls)	IDDM	15	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L)†	Reaction Time
Holmes et al.(98)	1986	Prospective single arm multiple condition (participants act as own controls)	Type 1	24	Euglycemia (6.1 mmol/L) Hypoglycemia (3.1 mmol/L)	Simple and complex reaction times
Herold et al.(99)	1985	Prospective single arm multiple condition* (participants act as own controls)	Type 1	12	Euglycemia (6.1–4.7 mmol/L) Hypoglycemia (2.5 mmol/L)†\	Reaction Time (custom system)
Holmes et	1983	Prospective single arm	Type 1	12	Euglycemia (6.1 mmol/L)	Memory tasks (Digit supraspan;

Reference	Year	Study Design	Type of diabetes	N=	Range of conditions tested	Relevant outcomes assessed
al.(100)		multiple condition* (participants act as own controls)			Hypoglycemia (3.1 mmol/L)	Rey auditory verbal learning test Attention tasks (MFFT; Delayed reaction time) Visual Spatial Task (BVRT) Academic Tasks (NDRT; mathematical computations)

* Study compared cognitive function in diabetics and non-diabetic controls. For Key Question 2, we are only interested in the diabetic cohort. Thus for the purposes of this question, this study is a single arm multiple condition study;

† Cognitive or psychomotor function assessed at several other conditions falling within these levels were assessed

BVRT=Benton Visual Retention Task; DVT=Digit Vigilance Task; IDDM=insulin Dependent Diabetes Mellitus; MCRTA=Multiple-Choice Reaction Time Apparatus; MFFT=Matching Familiar Figures Test; NDRT=Nelson Denny Reading Test; NES=Neurobehavioral Evaluation System; PSE=portosystemic encephalopathy; TMT A and B= Trial Making Test Parts A and B; VRT=Vienna Reaction Timer;

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Question 2 are presented in Table 19. This assessment found that the quality of all of the included studies was in the low to moderate range with all but one study being graded as moderate quality.

Table 19. Quality of Studies (Key Question 2)

Reference	Year	Quality Scale Used	Quality Score	Quality
Simulated driving studies				
Cox et al.(88)	2000	Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(101)	9.23	Moderate
Cox et al.(93)	1993	Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(101)	9.23	Moderate
Hoffman et al.(96)	1989	ECRI Quality Scale III-Before After Study	10.0	Moderate
Cognitive or psychomotor function studies				
Lobmann et al.(90)	2000	ECRI Quality Scale III-Before After Study	10.0	Moderate
Weinger et al.(91)	1999	ECRI Quality Scale III-Before After Study	10.0	Moderate
Dreisen et al.(92)	1995	ECRI Quality Scale III-Before After Study	8.18	Low
Blackman et al.(94)	1992	ECRI Quality Scale III-Before After Study	10.0	Moderate
Lingenfelser et al.(95)	1992	ECRI Quality Scale III-Before After Study	9.13	Moderate
Hoffman et al.(96)	1989	ECRI Quality Scale III-Before After Study	10.0	Moderate
Heller et al.(97)	1987	ECRI Quality Scale III-Before After Study	9.13	Moderate
Holmes et al.(98)	1986	ECRI Quality Scale III-Before After Study	10.0	Moderate
Herold et al.(99)	1985	ECRI Quality Scale III-Before After Study	9.13	Moderate
Holmes et al.(100)	1983	ECRI Quality Scale III-Before After Study	10.0	Moderate

Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that address Key Question 2 are presented in Table 20. None of the included studies examined the effects of hypoglycemia on simulated driving skills or cognitive and psychomotor function in a population of CMV drivers. Consequently, the degree by which the findings of the included studies, particularly findings related to specific driving skills, can be generalized to this group of professional drivers is unclear. Another important limitation of the generalizability of the included studies to CMV drivers is that no study enrolled individuals with type 2 diabetes. Given that the prevalence of type 2 diabetes in the general population is considerably higher than type 1 diabetes (see *Background* section), the fact that the findings of Key Question 1 suggest that type 2 diabetes (when controlled with insulin, oral agents, or both) may be just as important a risk factor (if not more important) for a motor vehicle crash than is type 1 diabetes, and the fact that it is not clear that the effects of hypoglycemia on cognitive performance, psychomotor function, and driving performance among individual with type 2 diabetes are comparable, the limitations of this evidence base are clear.

Table 20. Characteristics of Enrolled Patients (Key Question 2)

Reference	Year	Diabetes type	Number of individuals with diabetes included (n=)	Age distribution	Duration of diabetes	% Male	% CMV drivers	HBA1c (%)	IQ	BMI	Generalizability to target population
Driving performance studies											
Cox et al.(88,89)	2000	Type 1	37	Mean=35 .9 (SD=7.1) years Range=NR years	Mean=17.5 (SD=10.0) years Range=NR	43.2	NR	Mean=8.5 (SD=1.8) Range=NR	NR	Mean=35.3 (SD=7.3) Range=NR	Unclear
Cox et al.(93)	1993	Type 1	25	Mean=35 .9 (SD=14.2) years Range=NR years	Mean=14.6 (SD=10.5) years Range=NR	48.0	NR	Mean=10.8 (SD=2.9) Range=NR	NR	NR	Unclear
Hoffman et al.(96)	1989	Type 1	18	Mean=29.3 (SD=1.2) years Range=NR	Mean=7.7 (SD=1.6) years Range=NR	44.4	NR	Mean=6.9 (SD=1.3) Range=NR	NR	NR	Unclear
Cognitive and psychomotor function studies											
Lobmann et al.(90)	2000	Type 1	12	Mean=31 .0 (SD=7) years Range=20–43 years	Mean=7.8 (SD=8.6) years Range=1–29 years	58.3	NR	Mean=7.38 (SD=1.8) Range=NR	NR	Mean=24.2 (SD=3.9) Range=NR	Unclear
Weinger et al.(91)	1999	Type 1	60	Mean=33 .0 (SD=9) years Range=NR	Mean=9 .0 (SD=3) years Range=NR	50.0	NR	Mean=8.7 (SD=1.0) years Range=NR	NR	NR	Unclear
Dreisen et al.(92)	1995	Type 1	25	Mean=35.5 (SD=14) years Range=19–67 years	Mean=14.3 (SD=10.6) years Range=2–36 years	48.0	NR	Mean=10.6 (SD=0.58) Range=6–16.7	Mean=109 (SD=11) Range=90–137	NR	Unclear
Blackman et al.(94)	1992	Type 1	14	Mean=29.5 (SE=1.6) years Range=NR	Mean=15.2 (SE=2.0) years) Range=NR	42.8	NR	Mean=11.0 (SE=0.5) Range=NR	NR	Mean=23.8 (SE=0.5) Range=NR	Unclear
Lingenfelser et al.(95)	1992	Type 1	10	Mean=38.5 (SD=11.2) years Range=NR	Mean=10.5 (SD=4.3) years Range=NR	40.0	NR	Mean=9.5 (SD=1.1) Range=NR	NR	NR	Unclear
Hoffman et al.(96)	1989	Type 1	18	Mean=29.3 (SD=1.2) years Range=NR	Mean=7.7 (SD=1.6) years Range=NR	44.4	NR	Mean=6.9 (SD=1.3) Range=NR	NR	NR	Unclear

Reference	Year	Diabetes type	Number of individuals with diabetes included (n=)	Age distribution	Duration of diabetes	% Male	% CMV drivers	HBA1c (%)	IQ	BMI	Generalizability to target population
Heller et al.(97)	1987	Type 1	15	Mean=36.0 (SE=3.0) years) Range=NR	Mean=9.9 (SE=0.5) years Range=NR	80.0	NR	Mean=9.3 (SE=0.3) Range=NR	NR	NR	Unclear
Holmes et al.(100)	1986	Type 1	24	Mean=21.3 (SD=NR) years Range=18–35 years	Mean=8.2 (SD=NR) years Range=0.5–19 years	100.0	NR	Mean=9.6 (SD=NR) Range=5.9–12.9	Mean=112.6 (SD=1.9)	NR	Unclear
Herold et al.(99)	1985	Type 1	12	Mean=31.3 (SD=2.1) years Range=NR	Mean=10.1 (SD=2.4) years Range=NR	50.0	NR	Mean=10.8 (SD=0.9) Range=NR	NR	NR	Unclear
Holmes et al.(100)	1983	Type 1	12	NR	NR	50.0	NR	NR	NR	NR	Unclear

*Drivers with a history of a driving mishap; †Drivers with no history of a driving mishap; NA=Not applicable; NR=Not reported; SD=Standard deviation; SE=Standard error

Findings

Simulated Driving Studies

The findings of the three included studies that assessed the effects of hypoglycemia on simulated driving are summarized in Table 21. All three studies found that driving ability was impaired during hypoglycemia across several variables. Despite agreement across studies that driving ability is impaired by hypoglycemia, there is little agreement as to which aspects of driving become impaired and at what level of hypoglycemia these impairments begin to become manifest.

Table 21. Hypoglycemia and Simulated Driving Ability

Reference	Year	Simulator details	Measure of performance	Change from euglycemic condition (BG level 1)	Change from euglycemic condition (BG level 2)	Change from euglycemic condition (BG level 3)
Cox et al.(88)	2000	Atari Research Driving Simulator (3-screen version). Set up to simulate 16 miles of a typical grade 2 U.S highway.	*Condition (BG range)*	*4.0–3.3 mmol/L*	*3.3–2.8 mmol/L*	*<2.8 mmol/L*
			SD steering (z-score)	0.04 (*P*=NS)	−0.02 (*P*=NS)	−0.04 (*P*=NS)
			Off-road (z-score)	0.25 (*P*=NS)	0.45 (*P*=NS)	0.57 (*P*=NS)
			Risk midline (z-score)	**0.05 (NS)**	**0.17 (NS)**	**0.11 (P <0.01)**
			Low speed (z-score)	0.01 (*P*=NS)	−0.05 (*P*=NS)	0.37 (*P*=NS)
			High speed (z-score)	**0.23 (P <0.01)**	**0.56 (P <0.001)**	**0.26 (NS)**
			SD speed (z-score)	−0.09 (*P*=NS)	0.09 (*P*=NS)	0.23 (*P*=NS)
			Inappropriate braking (z-score)	0.00 (*P*=NS)	0.61 (*P*=NS)	0.00 (*P*=NS)
			Composite driving impairment score (z-score)	*0.83 (P <0.01)*	*1,83 (P <0.005)*	*1.52 (P <0.005)*
			% of patients significantly impaired	12	26	16
			Patient's impression of difficulty in driving (z-score)	*0.30 (P <0.05)*	*0.35 (P <0.01)*	*0.54 (P <0.01)*
			% of subjects who detected driving impairment (z-score)	21	22	25
			% of subjects who detected hypoglycemia (z-score)	15	33	79
			# subjects who took corrective action to treat hypoglycemia (z-score)	5	3	22
Cox et al.(93)	1993	Atari Research Driving Simulator (single screen version: low resolution 513 by 384 pixels) Participants underwent 4 4-minute tests a day for 2 days	*Condition*	*3.6+/-0.3 mmol/L*	*2.6+/-0.28 mmol/L*	
			Steering			
			Swerving (z-score)	*P*=NS	**P <0.03**	
			Spinning (z-score)	*P*=NS	**P <0.04**	
			Time across midline (seconds)	*P*=NS	**P <0.05**	
			Time off road (seconds)	*P*=NS	**P <0.01**	
			Speed Control			
			Speeding (seconds >10% speed limit)	*P*=NS	*P*=NS	
			Driving too slow (seconds <30% below speed limit	*P*=NS	**P <0.04**	
			Smooth acceleration	*P*=NS	*P*=NS	
			Smooth braking	*P*=NS	*P*=NS	

Reference	Year	Simulator details	Measure of performance	Change from euglycemic condition (BG level 1)	Change from euglycemic condition (BG level 2)	Change from euglycemic condition (BG level 3)
Hoffman et al.(96)	1989	M-8000A Driver Simulator System 3-video scenarios. Subject required to respond in simulator by adjusting speed and direction of simulated vehicle to avoid hazards. Errors automatically collected	Condition *Signaling, Steering and Acceleration* Performance poorer for several (n not reported) individuals during hypoglycemia	3.1 mmol/L *P*=NS		

Cognitive and Psychomotor Function Studies

The findings of the 10 included studies that evaluated cognitive and/or psychomotor function in individuals with diabetes are summarized in Table 22. Because no two studies assessed cognitive or psychomotor function using the same test, we have not attempted to pool the outcome data using meta-analysis. Instead we have summarized the findings of a qualitative analysis of the available outcome data.

The results of the 10 studies included in the table consistently demonstrate that moderate hypoglycemia has an acute deleterious effect on the ability of some individuals with insulin-dependent diabetes to perform a wide variety of cognitive and psychomotor tasks. At the present time no comparable data sets are available for individuals who do not require insulin to control their diabetes.

While on average, cognitive and psychomotor performance among individuals with type 1 diabetes were significantly impaired during moderate hypoglycemia, some individuals appeared to be unaffected by low blood glucose levels. Aside from a very limited history of hypoglycemic episodes, the defining characteristics of this latter group of individuals remain unclear.

Another group of individuals included in the studies demonstrated diminished or absent hypoglycemia awareness. These individuals were either unaware that they were hypoglycemic or they underestimated the impact that hypoglycemia was having on their cognitive and psychomotor function. For example, Weinger et al.(91) noted that several individuals in their study with moderate symptomatic hypoglycemia (blood glucose level approximately 2.2 mmol/L) stated that, if allowed, they could drive safely at that time. Heller et al.(97) noted that more than 70% of enrollees in their study were unaware that their blood glucose levels were clamped at 2.5 mmol/L (moderate hypoglycemia), yet all of these individuals demonstrated impaired reaction times. Clearly, these latter findings have important safety implications.

Table 22. Hypoglycemia and Cognitive and/or Psychomotor Function

Reference	Year	Findings	% who did not perceive onset of symptomatic hypoglycemia or believed that they were safe to drive
Lobmann et al.(90)	2000	*Test of Selective Attention (custom test)* Selective attention diminished as a function of increased hypoglycemia. Response times increased significantly during hypoglycemia (*P*= 0.006] and decreased significantly with restoration of euglycemia (*P* <0.001).	NR
Weinger et al.(91)	1999	*Trail Making Test Part B* Significant deterioration in test performance as a function of increasing hypoglycemia (P <0.001) *Choice Reaction Time* Significant deterioration in test performance as a function of increasing hypoglycemia (P <0.01) *Digital Vigilance Test* Significant deterioration in test performance as a function of increasing hypoglycemia (items scanned, *P* <0.001; omission errors, *P* <0.01) *Subtraction Test* Significant deterioration in test performance as a function of increasing hypoglycemia as measured by time (*P* <0.001) but not score (p=NS).	22% considered themselves safe to drive when blood glucose level was ≤2.2 mmol/L (severe hypoglycemia). None of these individuals demonstrated serious cognitive impairment at these blood glucose levels. 12% of individuals with severe hypoglycemia stated that they could drive safely 12% of individuals demonstrated hypoglycemia unawareness.
Dreisen et al.(92)	1995	*Reaction Time (Simple)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.68, P <0.05) *Reaction Time (Choice Side)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.59, P <0.05) *Reaction Time (Choice Direction)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.55, P <0.05) *Reaction Time (Complex Side)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.58, P <0.05) *Reaction Time (Complex Direction)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.44, P <0.05)	NR
Blackman et al.(94)	1992	*Reaction Time* Reaction time increased significantly (P <0.001) during hypoglycemia (2.5 mmol/L).	21.4% of enrollees reported that they did not experience symptoms of hypoglycemia when blood glucose levels clamped at 2.5 mmol/L. Whether these three individuals demonstrated slowed reaction times was not reported.
Lingenfelser et al.(95)	1992	*Digit Symbol Test* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.05). *Digit Connection Test* No significant change in performance observed. *Aiming Center I* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.01). *Aiming Center II* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.01). *Line Tracing Time* No significant change in performance observed. *Line Tracing Errors*	40% of enrollees were unaware of the fact that they were hypoglycemic (blood glucose level clamped at 2.2 mmol/L).

Reference	Year	Findings	% who did not perceive onset of symptomatic hypoglycemia or believed that they were safe to drive
		Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.01). *Reaction Time* Significant deterioration in test performance as a function of increasing hypoglycemia observed *(P* <0.01).	
Hoffman et al.(96)	1989	*Reaction Time* Reaction time slower during hypoglycemia. However, considerable variation was seen and overall effect failed to reach significance (P=0.126) *Trail Making Test Part A and B* Significant reduction in Trail Making Part B (but not A) in performance during hypoglycemia (P=0.002) *Pursuit Rotor Performance* Significant reduction in pursuit-rotor performance during hypoglycemia (P=0.007).	NR
Heller et al.(97)	1987	*Reaction Time* Significant deterioration in test performance as a function of increasing hypoglycemia observed *(P* <0.01).	73.3% of enrollees unaware of hypoglycemia (blood glucose clamped at <2.5 mmol/L). All individuals demonstrated prolonged reaction times.
Holmes et al.(98)	1986	*Simple Reaction Time* No significant effect *Go/No-Go Reaction Time* Significant reduction in performance during hypoglycemia (P <0.05) *Choice Reaction Time* Significant reduction in performance during hypoglycemia (P <0.05)	NR
Herold et al.(99)	1985	*Reaction Time* Mean reaction time increased significantly during hypoglycemia when compared to euglycemic state (*P* <0.02). The range of individual responses was wide. 5 of 12 individuals did not demonstrate increases in reaction time.	16.6% of enrollees unaware of hypoglycemia (blood glucose levels clamped at approx. 2.4 mmol/L) Both individuals demonstrated prolonged reaction times.
Holmes et al.(100)	1983	*Digit supraspan* No significant effect *Rey auditory verbal learning test* No significant effect *MFFT* No significant effect *Delayed reaction time* Significant reduction in performance during hypoglycemia (P <0.05) *BVRT* No significant effect *NDRT* No significant effect *Mathematical computations* Significant reduction in performance during hypoglycemia (P <0.05)	NR

Section Summary

The conclusions of our assessment of the evidence addressing Key Question 2 are presented below. Note that none of the included studies examined the effects of

hypoglycemia on simulated driving ability, cognitive or psychomotor function in a group of CMV drivers with diabetes. Also, note that all of the included studies examined the effects of hypoglycemia in individuals with type 1 diabetes only. No individuals with type 2 diabetes were enrolled in any included study. Even if current interstate restrictions on CMV drivers with insulin-treated diabetes are lifted, non-insulin treated individuals with type 2 diabetes will still comprise the vast majority of CMV operators who have the disorder. Consequently, the degree to which the findings of the included studies, particularly findings related to specific driving skills, can be generalized to CMV operators is unclear.

1. **Hypoglycemia has a significant deleterious effect on the driving ability of some individuals with type 1 (or IDDM) when measured using a driving simulator (Strength of Evidence: Moderate).**

   - **Due to a paucity of data (only two studies), no attempt was made to determine a quantitative estimate of the relationship between the deterioration in driving competency and blood glucose levels.**

   Three small (total N=80), moderate-quality studies assessed the effects of induced hypoglycemia on simulated driving ability. All three studies found that driving ability was impaired during hypoglycemia across several variables. Despite agreement across studies that driving ability is impaired by hypoglycemia, there is little agreement as to exactly which aspects of driving ability are most vulnerable to hypoglycemia and at what levels of hypoglycemia these impairments begin to become manifest.

2. **Hypoglycemia has a significant deleterious effect on the cognitive and psychomotor function of individuals with type 1 (or IDDM) as measured by a number of different tests of cognitive function (Strength of Evidence: Moderate)**

   - **Due to the fact that no more than two studies used the same tests of cognitive or psychomotor function, no attempt was made to determine a quantitative estimate of the relationship between functional loss and blood glucose levels.**

   Ten small (Total N=202) low-to-moderate quality studies assessed the effects of induced hypoglycemia on cognitive and psychomotor function. These 10 studies consistently demonstrated that moderate hypoglycemia had an acute deleterious effect on the ability of some (but not all) individuals with insulin-dependent diabetes to perform a wide variety of cognitive and psychomotor tasks. At the present time no comparable data sets are available for individuals who do not require insulin to control their diabetes.

   The 10 included studies consistently demonstrate that moderate hypoglycemia (blood glucose levels in the region of 2.5-3.0 mmol/L[45–54 mg/dl]) has a deleterious acute effect on the ability of some individuals with type 1 diabetes to perform a wide variety of cognitive and psychomotor tasks. While on average, cognitive and psychomotor performance was significantly impaired during moderate hypoglycemia, some individuals appeared not to be affected by these levels of hypoglycemia. Other individuals appeared to be unaware that they were hypoglycemic and/or they tended

to underestimate the impact that hypoglycemia was having on their cognitive and psychomotor function. For example, Weinger et al.(91) noted that 12% of the individuals in their study demonstrated hypoglycemia unawareness and several individuals with severe hypoglycemia stated that, if allowed, they could drive safely. Heller et al.(97) noted that over 70% of enrollees in their study were unaware that their blood glucose levels were clamped at 2.5 mmol/L (moderate hypoglycemia), yet all of these individuals demonstrated impaired reaction times.

Key Question 3: What treatment-related factors are associated with an increased incidence of severe hypoglycemia among drivers with diabetes mellitus?

The primary aim of modern treatments for individuals with diabetes is to control blood glucose levels at near normal levels. This is because studies have shown that maintaining tight control reduces the risk for developing the long-term complications associated with type 1 and type 2 diabetes (retinopathy, nephropathy, neuropathy, cardiovascular disease, etc.).(102-107) The primary limiting factor for attaining tight control of blood glucose levels is hypoglycemia. Consequently, much effort has been exerted in the development of new drugs (e.g., meglitinides, thiazolidinediones, etc.), treatment regimes (e.g., combinations of long acting and short acting insulin), and treatment delivery methods (e.g., insulin pumps) that allow tight control while minimizing the risk for hypoglycemia.

In this section of the evidence report, we attempt to determine which treatment-related factors are associated with an increased risk for severe hypoglycemia. The purpose of this analysis is to determine whether there is any evidence that some treatment options, treatment regimes, or treatment delivery methods present less of a risk for the development of severe hypoglycemia than others. The treatment options we consider in this evidence report are those listed in Table 2 of the *Background* section of this evidence report. This comprehensive list covers all currently available treatment options in the United States that have FDA approval for marketing. We do not consider treatment options that are currently considered experimental (because a significant proportion of experimental treatment options will never make it to market) or those that are no longer available.

Several investigators have attempted to identify risk factors for severe hypoglycemia among individuals with diabetes. Findings from these studies are presented in Table 23. Figure 12 shows that a number of behavioral, demographic, and treatment-related factors were consistently identified as being associated with an increased incidence of hypoglycemia. Although several treatment-related risk factors have been consistently identified they are not helpful in addressing Key Question 3 because they tell us what we already know—the tighter the control of blood glucose levels, the higher the risk for hypoglycemia. As stated above, the intent of this section is to determine whether there are treatment options available that allow tight control of blood glucose levels while minimizing the risk for hypoglycemia. Consequently, we must look for evidence elsewhere.

Table 23. Significant Risk Factors for Severe Hypoglycemia

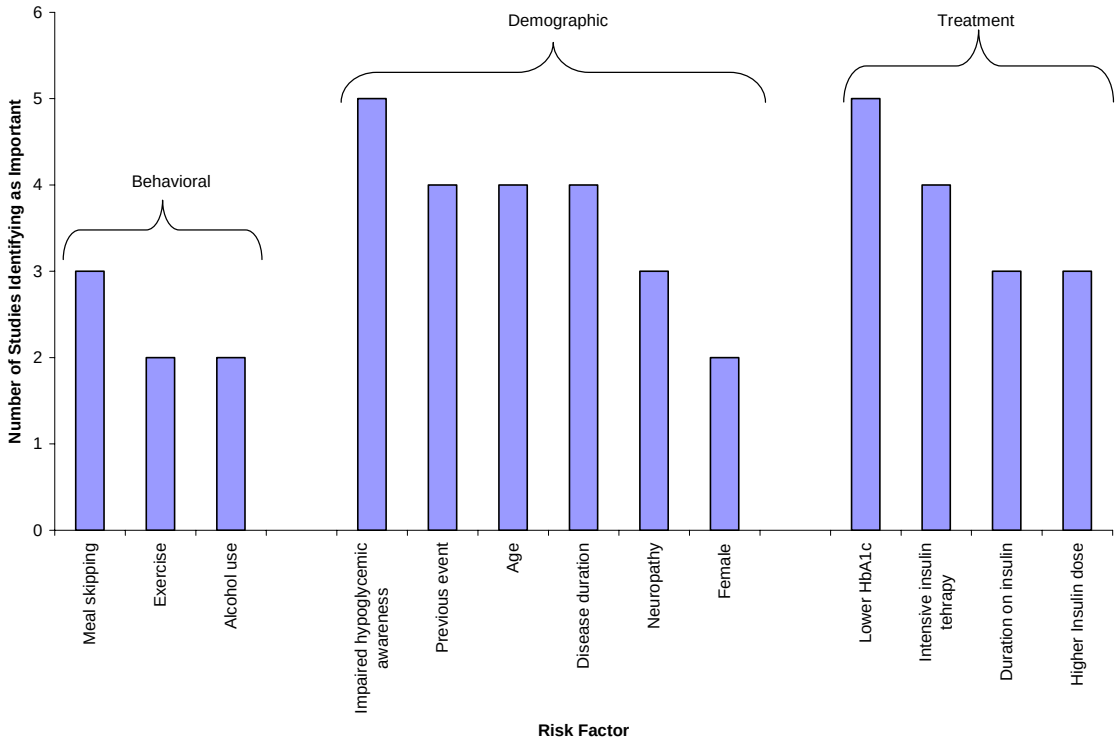
Reference	Year	N=	Diabetes Type	Study details	Definitions used	Risk factors identified
Murata et al.(108)	2005	344	Type 2	Prospective cohort study (1 year) Primary endpoint = clear relationship between a factor and occurrence of a mild or severe hypoglycemic event in previous year (self-reported)	Mild hypoglycemia = mild to moderate symptoms including palpitations, diaphoresis, weakness or anxiety. Severe hypoglycemia = severe symptoms affecting mentation or requiring the assistance of others.	*Mild hypoglycemia* • Recent increase in medication dose • Excessive dieting or weight loss • Missed meal • Wrong medication dose • Concurrent illness • Exercise *Severe hypoglycemia* • Excessive dieting or weight loss • Missed meal • Wrong medication dose
Donnely et al.(18)	2004	267	Type 1 and Type 2	Prospective Ordinal logistic regression was performed to identify potential predictors of hypoglycemia. Primary outcome = moderate or severe hypoglycemic events occurring in during 1-month (self-reported)	Mild hypoglycemia = mild to moderate symptoms requiring remedial action. Severe hypoglycemia = severe symptoms affecting mentation or requiring the assistance of others.	*Moderate or severe hypoglycemia* • Type of diabetes (Type 1 higher risk) *Type 1 diabetes* • Event in previous month • Concurrent use of any other drug • Insulin dose *Type 2†: diabetes* • Event in previous month • Duration of insulin use
Pederson-Bjergaard et al.(30)	2004	1076	Type 1	Survey (retrospective) Multicenter: UK and Denmark (4 centers) Primary outcome = severe hypoglycemic events occurring in previous year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma.	*Univariate factors* • Age • Duration of diabetes • Female sex • HbA_{1c} • Presence of diabetic neuropathy • Impaired hypoglycemic awareness • Absent hypoglycemic awareness • Single or divorced • Use of alcohol • Smoking *Multivariate factors* • Reduced hypoglycemia awareness‡; • Symptomatic peripheral neuropathy‡; • Smoking‡

Reference	Year	N=	Diabetes Type	Study details	Definitions used	Risk factors identified
Allen et al.(109)	2001	415	Type 1	Prospective study Demographic and self management measures taken All pts had history of diabetes >4.5 years Frequency and severity of hypoglycemia self reported		*Frequency of hypoglycemia (univariate)* • Low $HbA1_c$ • Intensive insulin therapy • Frequency of blood glucose measurement in a day • Age • White race • Mothers education *Frequency of Severe hypoglycemia (univariate)* • Low $HbA1_c$ • Frequency of blood glucose measurement in a day • Age • Female sex • Medicaid vs other *Frequency of hypoglycemia (multivariate)* • Low $HbA1_c$ • Intensive insulin therapy (among those aged >15) • Frequent blood glucose monitoring *Frequency of severe hypoglycemia (multivariate)* • Low $HbA1_c$ • Intensive insulin therapy (all ages)
Ter Braak et al.(32)	2000	195	Type 1	Retrospective clinical survey of consecutive patients using a questionnaire Primary outcome = severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma	*Univariate factors* • Presence of neuropathy • Worry about hypoglycemia • Reduced hypoglycemic awareness *Multivariate factors* • Presence of nephropathy • Reduced hypoglycemic awareness • Insulin dose >0.1 U/kg higher
Muhlhauser et al.(33)	1998	684	Type 1	Prospective population based survey Primary outcome = the number of severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma	*Multivariate factors* • Severe hypoglycemia in preceding year • Severe hypoglycemia anytime in the past • C-peptide negativity • Social status • Patient drive to attain normoglycemia

Reference	Year	N=	Diabetes Type	Study details	Definitions used	Risk factors identified
Bott et al.(34)	1997	636	Type 1	All patients were on intensive insulin therapy Primary outcome = the number of severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = hypoglycemia requiring treatment with IV glucose or glucagon injection	*Multivariate factors* • Lower HbA_{1c} during follow up • Severe hypoglycemia in preceding year • C-peptide levels >0.1nmol/L • Younger age at onset of disease • Not carrying emergency glucose • Poorer scores on coping scale
Gold et al.(35)	1997	60	Type 1	Prospective Primary outcome = the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using structural equation modeling	Severe hypoglycemia = help required from others or hypoglycemic coma	*Multivariate factors* • Previous hypoglycemia • Age • Duration of disease • Reduced autonomic function • Reduced hypoglycemic awareness
Shorr et al.(21)	1997	19,932	Type 1 and Type 2 On insulin or sulfonylureas (≥65 years old- Medicaid population)	Prospective Primary outcome = the number of serious hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using multivariate regression	Serious hypoglycemia = event that occurred outside of hospital that resulted in a visit to an emergency department, admission to hospital, or death	*Multivariate factors* • Age • Time since discharge from hospital • African-American race • Concomitant use of ≥5 medications • New hypoglycemic drug therapy
Pampanelli et al.(36)	1996	112	Type 1 (all IIT)	Prospective Primary outcome=the number of severe hypoglycemic episodes during a 13 year period Data analyzed using univariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• Lower HbA_{1c} • Reduced autonomic function • Reduced hypoglycemic awareness
Bell et al.(37)	1994	211	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Case-control design	Severe hypoglycemia = help required from others or hypoglycemic coma	• Duration of disease • Number of insulin injections per day • Number of glucose tests per day • Presence of neuropathy and nephropathy • Use of animal insulin • Meal skipping;
EURODIAB(110)	1994	3,250	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using multivariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• Duration of disease • Tight control

Reference	Year	N=	Diabetes Type	Study details	Definitions used	Risk factors identified
MacLeod et al.(19)	1993	600	Type 1 (n=544) Type 2† (n=54)	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using multivariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• History of hypoglycemia • History of hypoglycemia-related injury • Duration of insulin therapy • Frequency of outpatient reviews
Mulhauser et al.(29)	1991	90	All Type 1 Impaired kidney failure: (n=44)	Retrospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Case-control design	Severe hypoglycemia = hypoglycemia with loss of consciousness	• Impaired kidney function • Among patients with kidney impairment • Low BMI
Ward et al.(41)	1990	158	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 2 years (self-reported) Data analyzed using ANOVA	Severe hypoglycemia = help required from others or hypoglycemic coma	• None identified
Casparie & Elving(20)	1985	400	Type 1 (n=200) Type 2 (n=200) All treated with insulin	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma	• Type of Diabetes (Type 1 highest risk) • Low $HbA1_c$ • High dose of insulin
Goldgewicht et al.(111)	1983	172	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 to 5 years (self-reported) Data analyzed using univariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• Duration of diabetes • Duration on insulin • Body mass index • Frequency of urine sample analysis • Frequency of blood sample analysis

Figure 12. Frequency Factor Identified as a Risk Factor for Hypoglycemia



Identification Evidence Base

The most appropriate study designs for the evaluation of risk factors associated with a particular condition among representative populations while controlling for other known risk factors come from epidemiology. Consequently, our searches focused on identifying epidemiological studies (case-control studies or cohort studies) that attempted to determine the relative risk for hypoglycemia that is associated with different treatment options, different treatment regimes, or different modes of treatment administration.

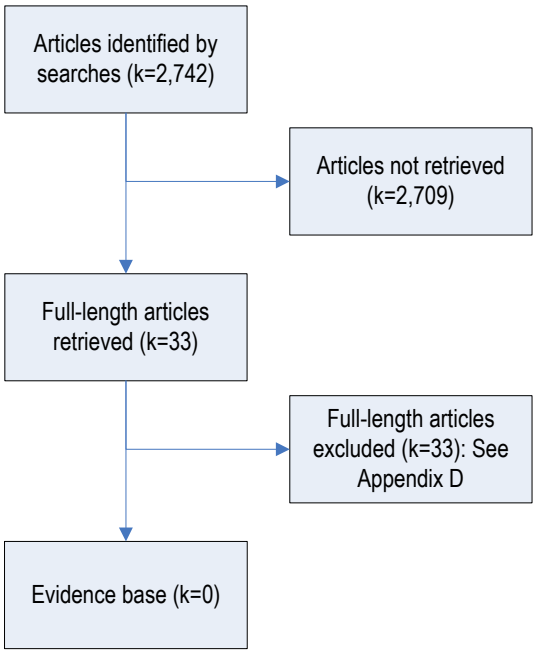
Most available information on the frequency of the occurrence of hypoglycemia among patients who undergo treatment for diabetes comes from efficacy and safety studies (usually randomized controlled trials). Although randomized controlled trials (RCTs) are often considered, "the gold standard cohort study," when used to assess treatment efficacy and safety of a treatment, RCTs have a number of shortcomings, including the following:

1. Safety and effectiveness trials tend to enroll carefully screened and selected patients who are not representative of the broader population.
2. Safety and efficacy trials use protocols that are not reflective of disease management in the broader population.
3. Safety and effectiveness trials tend to be small and short-term, which precludes an accurate determination of the true incidence of hypoglycemia.

In order to ensure that any assessment of the available evidence addressing Key Question 3 was meaningful we developed restrictive retrieval and inclusion criteria that were designed to exclude studies that suffer from the shortcomings described above. As a consequence, several thousand articles were screened but not retrieved because they were either not generalizable to the broader population, they utilized protocols that were not reflective of how treatment would be used in clinical practice, or they were small or used a short follow up time that precluded accurate estimation of the incidence of hypoglycemia. Readers who wish to consider data on the occurrence rates for hypoglycemia observed in clinical trials that have evaluated the effectiveness and safety of currently available drugs are directed to the extensive list of systematic reviews in Table J-1 of Appendix J.

The development path of the evidence base for Key Question 3 is summarized in Figure 13. In total, our searches (Appendix A) identified a total of 2,742 articles that appeared to have relevance to this key question. Following application of the *a priori* retrieval criteria for this question (see Appendix B for retrieval criteria), only 33 full-length articles were retrieved and read in full. Of these 33 retrieved articles, none was found to meet the inclusion criteria for Key Question 3 (see Appendix C for inclusion criteria).

Figure 13. Development of Evidence Base for Key Question 3



Evidence Base

No studies met the inclusion criteria for this question.

Findings

No studies met the inclusion criteria for this question

Section Summary

No studies were identified that met the inclusion criteria for this evidence report. Consequently, we have not answered Key Question 3.

Known treatment-related risk factors for an increased incidence of severe hypoglycemia include lower HbA1c, the use of insulin, and intensified insulin treatment (multiple injections per day). The aim of this question was to determine the effect of specific treatment options (different types of insulin, different types of oral hypoglycemic agents, different treatment combinations) on the incidence of severe hypoglycemia among individuals with diabetes.

Although our searches identified a large number of RCTs that provided data on the proportion of individuals enrolled in the study who experienced hypoglycemia and a number of studies on the risk factors associated with hypoglycemia, none met the inclusion criteria for this key question.

Key Question 4: How effective is Blood Glucose Awareness Training in preventing the consequences of hypoglycemia?

In this section of the report, we evaluate the evidence pertaining to the effectiveness of Blood Glucose Awareness Training (BGAT). BGAT, which was developed by Cox and his colleagues at the University of Virginia, is a psychoeducational intervention program designed to assist individuals with type 1 diabetes in managing and maintaining tight diabetic control.(112) According to the program's developers, individuals need accurate information about how their insulin, dietary choices, and physical activity levels affect their blood glucose in order to effectively manage their diabetes.(112) In addition, it is argued that for individuals with diabetes to manipulate these factors to achieve euglycemic balance, they must know where their blood glucose level is and be able to determine which direction it is going. For example, a blood glucose level of 3.3 mmol/L (60 mg/dl) that is rising may need no intervention, but a blood glucose level of 3.5 mmol/L (65 mg/dl) that is rapidly falling may require immediate intervention in order to avoid hypoglycemia.

BGAT is an eight-week program centered on a manual[19] that consists of eight distinct units. Unit 1 focuses on how to apply BGAT to daily life through homework, including making use of a blood glucose awareness diary. Patients observe and recording any blood glucose-relevant cues in the diary, estimate their perceived blood glucose level based on these cues, compare these estimates to an actual measured blood glucose level, and then calculate the accuracy of their estimated blood glucose level using an error grid. This process is repeated throughout BGAT with the aim of refining the accuracy of the patient's perceived blood glucose level. Units 2 through 4 of the BGAT program focus on the recognition and interpretation of three critical aspects of blood glucose self management—carbohydrate counting, insulin kinetics, and metabolic equivalents of physical activity—thereby providing the patient with a better understanding of why their

[19] Five different versions of the BGAT manual have been published (BGAT-1, BGAT-2, HAATT, BGAT-3, and BGATHome.com). Despite differences between the two manuals, the basic structure of the program remains the same. The most obvious differences in the programs result from a progressive inclusion of items such as observation of external cues, implementation of newer insulin therapies as they became available, and an emphasis on long term BG maintenance.

blood glucose level is where it is and what changes in this level are likely to occur in the near future. Units 5 through 7 aim to teach users to recognize and interpret internal indicators of blood glucose extremes (autonomic symptoms, glycopenic symptoms, mood changes, etc.). Unit 8 summarizes what has been learned during the previous seven weeks of the program and promotes relapse prevention.

Based on additional research, Cox and his colleagues adapted BGAT(113-115) into the "Hypoglycemia Anticipation, Awareness and Treatment Training (HAATT)" program.(112,116) Like its predecessors, HAATT is an eight-unit program; however, HAAT differs from BGAT-1 and BGAT-2 in that it is focused specifically on treating individuals suffering from recurrent severe hypoglycemia. HAATT and BGAT were later consolidated into a single program, BGAT-3.

According to Cox,(112) a major barrier to the dissemination of BGAT and HAATT is the availability of training and materials. Consequently, Cox and his colleagues transformed the program so that it could be delivered on the internet (www.BGATHome.com). Unlike previous iterations of BGAT, BGATHome.com is a seven (not eight) unit program. Each unit of this interactive program takes between 15 to 60 minutes to complete.

Identification Evidence Base

The development path of the evidence base for Key Question 4 is summarized in Figure 14. Our searches (Appendix A) identified a total of 82 articles that appeared to be relevant to this key question. Following application of the *a priori* retrieval criteria for this question (Appendix B), 26 full-length articles were retrieved and read in full. Of these 26 retrieved articles, seven articles were found to meet the inclusion criteria for Key Question 4 (Appendix C). Table D-4 of Appendix D lists the 19 articles that met the *a priori* retrieval criteria for this question but that were found, on reading the full-length article, not to meet the inclusion criteria for this key question. Table 24 lists the seven articles that met the inclusion criteria for Key Question 4.

Figure 14. Development of Evidence Base for Key Question 4

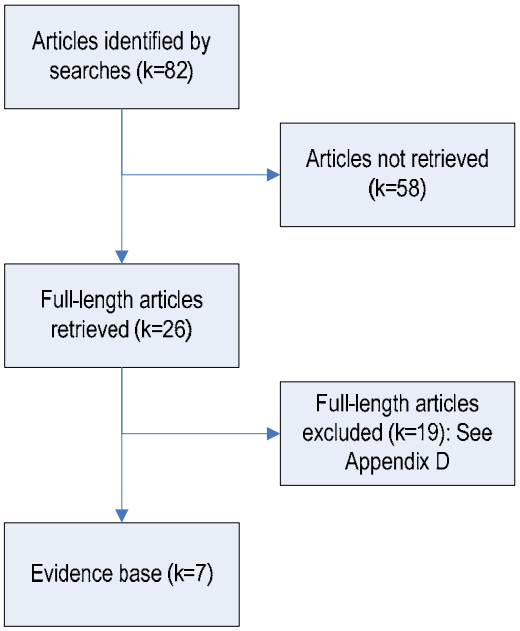


Table 24. Evidence Base for Key Question 4

Reference	Year	Form of BGAT studied	Study Site(s)	Country
Schachinger et al.(117)	2005	BGAT-2	Basal University Hospital; Olten Diabetes Clinic; Bad Mergentheim; Diabetes Outpatient Center Practice; Solurthurn Diabetes Outpatient Clinic; Aarau Diabetes Outpatient Clinic; Kanton Hospital Lozern	Switzerland and Germany
Cox et al.(116)	2004	HAATT	Medical University of Sofia, Sofia; Medical University of Varna, Varna; District Hospital, Russe	Bulgaria
Broers et al.(118,119)	2002	BGAT-1	Leiden University Medical Center, Leiden	Netherlands
Kinsley et al.(120)	1999	BGAT-1	The Joslin Diabetes Center, Boston, Massachusetts	USA
Cox et al.(121)	1991	BGAT-1	University of Virginia Health Sciences Center, Charlottesville, Virginia	USA
Cox et al.(122)	1989	BGAT-1	University of Virginia Health Sciences Center, Charlottesville, Virginia	USA
Cox et al.(123)	1988	BGAT-1	University of Virginia Health Sciences Center, Charlottesville, Virginia	USA

Evidence Base

This subsection provides important details on the studies that comprise the evidence base for Key Question 4 (Table 24). These details include the designs of the studies that have addressed this key question, the findings of our assessment of the quality of these studies, and information on the characteristics of the individuals that were enrolled in these studies. Those readers who require a more detailed description of the studies that are included in the evidence base for Key Question 4 are directed to the *Study Summary Tables* that are in Appendix E of this document.

Study Design Details

The design details of interest of the seven included studies that address Key Question 4 are presented in Table 25. All seven included studies that addressed Key Question 4 were prospective. Included studies used one of two general designs; randomized controlled trials (*k*=5) and non-randomized controlled trials (*k*=2). Two of the included studies were multicenter studies.

Table 25. Design of Included Studies (Key Question 4)

Reference	Year	Form of BGAT studied	Size (N=)	Prospective?	Randomized?	Multicenter? (If yes, # centers	Blinding Status	BGAT Attrition Rate (%)	Control Attrition Rate (%)	Follow up time (months)
Schachinger et al.(117)	2005	BGAT-2	138	Y	Y	Yes – 6	NR	23%	23%	12
Cox et al.(116)	2004	HAATT	60	Y	Y	Yes – 3	NR	NR	NR	12
Broers et al.(118,119)	2002	BGAT-1	59	Y	N	N	N	28%	22%	12
Kinsley et al.(120)	1999	BGAT-1	47	Y	Y	N	NR	NR	NR	1
Cox et al.(121)	1991	BGAT-1	39	Y	Y	N	NR	NR	NR	2
Cox et al.(122)	1989	BGAT-1	22	Y	Y	N	NR	NR	NR	>1
Cox et al.(123)	1988	BGAT-1	16	Y	N	N	NR	NR	NR	>1

Quality of Evidence Base

The findings of our assessment of the quality of each of the seven included studies are presented in Table 26. Two included studies, the studies of Broers et al.(118,119) and Schachinger et al.,(117) were found to be particularly susceptible to bias. Neither study demonstrated that they were protected against selection bias (a lack of comparability of individuals allocated to different arms of a study). Despite the fact that the study of Schachinger et al. was randomized, the comparability of treatment groups was compromised by a number of factors (high attrition rates, differential attrition, and evidence of possible randomization failure [non-comparability at baseline despite randomization]). As a consequence of the high potential for selection bias, one cannot have confidence that any between-group difference in outcome observed by either study was the result of BGAT. Such differences could simply be the result of systematic differences in the characteristics of the individuals enrolled in the two groups. As a result, we do not consider these two studies any further in this evidence report.

Table 26. Quality of Included Studies (Key Question 4)

Reference	Year	Form of BGAT studied	Quality Scale Used	Group Comp. Score	Acceptable group comparability?	Quality Score	Quality
Schachinger et al.(117)	2005	BGAT-2	EQS-I	4.58	No		
Cox et al.(116)	2004	HAATT	EQS-I	6.04	Yes	6.20	Moderate
Broers et al.(118,119)	2002	BGAT-1	EQS-I	1.88	No		
Kinsley et al.(120)	1999	BGAT-1	EQS-I	7.29	Yes	6.80	Moderate
Cox et al.(121)	1991	BGAT-1	EQS-I	8.75	Yes	7.50	Moderate
Cox et al.(122)	1989	BGAT-1	EQS-I	8.13	Yes	7.20	Moderate
Cox et al.(123)	1988	BGAT-1	EQS-I	5.00	Yes	5.70	Low
Overall quality of evidence base (median quality score)						**6.80**	**Moderate**

EQS-I=ECRI Quality Scale-I (for comparative trials)

Generalizability of Evidence to Target Population

The degree to which the findings of the studies that comprise the evidence base for Key Question 4 may be generalized to individuals with diabetes that might consider a career as an interstate CMV operator is unclear.

Enrollment in all five of the studies that address Key Question 4 was restricted to individuals with type 1 diabetes. Since hypoglycemic unawareness affects individuals with type 1 diabetes almost exclusively, the fact that BGAT has not been studied in populations of individuals with type 2 diabetes is to be expected.

Other important aspects of the patients enrolled in the included studies are presented in Table 27. As evidenced by the incompleteness of the table, the reporting of the characteristics of the enrollees in these five studies was poor, especially in the older studies. Basic patient demographic information such as age and sex were not consistently reported. Characteristics of particular interest to diabetes research such as Mean HbA_{1c}, body-mass index, mean duration of disease, and mean daily insulin intake were also inconsistently reported. From the information that was reported it appears that the majority of the patients enrolled in the included studies were between 23 and 49 years old with males making up 33% to 54% of trial participants. No information on the employment status of study enrollees was presented.

Table 27. Characteristics of Enrollees (Key Question 4)

Reference	Year	Treatment group	Sample size: n=	Mean age (SD): yrs	Mean duration of disease (SD): yrs	% Male	Mean HbA_{1c} (SD)	Mean daily insulin intake (SD): U/kg	BMI	Generalizability
Cox et al.(116)	2004	Overall	60	38.06 (9.27)	13.96 (8.93)	53.0	8.04 (0.74)	44.75 (14.13)	23.17 (3.26)	Unclear
		BGAT	30	37.60 (9.00)	13.93 (9.33)	53.0	8.08 (0.74)	46.63 (14.91)	23.61 (3.44)	
		Control	30	38.62 (9.76)	14.00 (7.64)	54.0	7.98 (0.70)	42.30 (12.96)	22.63 (2.99)	
Kinsley et al.(120)	1999	Overall	47	34.0 (8.0)	9.0 (3.0)	48.9	9.0 (1.2)	NR (NR)	25 (3.0)	Unclear
		BGAT	25	NR (NR)	NR (NR)	NR	9.1 (1.4)	NR (NR)	NR (NR)	
		Control	22	NR (NR)	NR (NR)	NR	9.0 (1.1)	NR (NR)	NR (NR)	
Cox et al.(121)	1991	Overall	39	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	Unclear
		BGAT (Standard)	13	33.7 (NR)	13.0 (NR)	38.5	10.4 (NR)	0.65 (NR)	NR (NR)	
		BGAT (Intensive)	12	31.1 (NR)	12.7 (NR)	33.3	12.8 (NR)	0.67 (NR	NR (NR)	
		Control	14	33.8 (NR)	11.2 (NR)	35.7	11.4 (NR)	0.62 (NR)	NR (NR)	
Cox et al.(122)	1989	Overall	22	32.4 (8.5)	10.6 (7.7)	36.4	NR (NR)	NR (NR)	NR (NR)	Unclear
		BGAT	15	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	
		Control	7	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	
Cox et al.(123)	1988	Overall	20	43.7 (NR)	10.3 (NR)	40.0	NR (NR)	NR (NR)	NR (NR)	Unclear
		BGAT	10	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	
		Control	10	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	

*Before-after study; BGAT=blood glucose awareness training; NR=not reported

Findings

The five included studies and the outcomes that they reported on are listed in Table 28. Outcome data were available for only two of the outcomes of interest to us. Data on sensibility to driving capability while impaired and the incidence of motor vehicle crash were not presented by any of the included studies. Of the two remaining outcomes of interest, two studies provided data on the incidence of severe hypoglycemia following BGAT and all five studies reported on the accuracy with which individuals with type 1 diabetes could estimate their blood glucose levels based on internal cues.

Table 28. Outcomes Assessed (Key Question 4)

Reference	Year	Outcomes of interest			
		Crash	Sensibility to driving capability while impaired	Incidence of severe hypoglycemic episodes	Blood glucose level accuracy index
Cox et al.(116)	2004			√	√
Kinsley et al.(120)	1999			√	√
Cox et al.(121)	1991				√
Cox et al.(122)	1989				√
Cox et al.(123)	1988				√
Total Number of Studies =		**0**	**0**	**2**	**5**

Blood Glucose Level Accuracy Index

All five included studies reported on the effect of BGAT on the ability of an individual with type 1 diabetes to accurately estimate blood glucose levels. Relevant results from these studies are presented in Table 29. Because the outcome data from three of the five studies were poorly presented, we have not attempted to calculate a precise estimate of the effectiveness of BGAT in improving the accuracy of blood glucose level estimation. Accordingly, our analysis of the available evidence pertaining to this outcome is purely qualitative.

Four of the five included studies, all authored by Cox, found that BGAT was effective in improving the ability of individuals with type 1 diabetes to accurately estimate their blood sugar levels based on internal cues alone.(116,121-123) The remaining study (Cox was listed as a co-author for this study) found no difference in the ability of individuals who had undergone BGAT to accurately estimate their blood glucose levels when compared with controls.(120) However, the authors of the study reported that individuals who underwent BGAT demonstrated significantly greater improvements in their ability to detect low blood glucose levels. Consequently, the available evidence, though not strong, does consistently suggest that BGAT is effective in improving the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels. Whether this improvement in the ability to estimate blood glucose levels has the net effect of reducing the incidence of sever hypoglycemia is addressed below.

Table 29. Effect of BGAT on Ability to Accurately Estimate Blood Glucose Levels

Reference	Year	Cohort	Blood Glucose Estimation Accuracy		Comments and Conclusions
			Mean (SD or SEM)	*P(between grps)*=	
Cox et al.(116)	2004	HAATT	*Reduction in extreme BG fluctuations* Mean BG Risk Index: 12.8 (SD: 4.05) % accuracy of BG evaluation: 82%	<0.01 <0.001	Evidence supports contention that HAATT awareness training may improve BG estimation accuracy.
		SMBG	*Reduction in extreme BG fluctuations* Mean BG Risk Index: 17.9 (SD: 4.74) % accuracy of BG evaluation: 73%		
Kinsley et al.(120)	1999	BGAT	At 3.3mmol/L: error=−3.7 (SEM: 1.2) At 2.8 mmol/L: error=−2.4 (SEM: 0.9) At 2.2 mmol/L: error=−1.1 (SEM: 0.5)	NS for any comparison BGAT had fewer undetected low BG readings compared to controls (P <0.05)	No evidence to support contention that BGAT improves overall blood glucose level awareness any more than a non-specific control. However, those subjects who underwent BGAT had fewer undetected low BG readings compared to controls.
		Cholesterol Ed.	At 3.3mmol/L: error=−3.7 (SEM: 1.1) At 2.8 mmol/L: error=−2.1 (SEM: 0.9) At 2.2 mmol/L: error=−1.0 (SEM: 0.4)		
Cox et al.(121)	1991	Standard BGAT	Mean Accuracy Index=NR (SEM: NR)	Time effect: *P* <0.0001 Group * Time interaction: *P* <0.001 S-BGAT vs I-BGAT: *P*=0.17	Evidence that BGAT awareness training may improve BG estimation accuracy when compared to non-specific control group. There was no significant difference between standard BGAT and intensive BGAT in improving BG estimation accuracy.
		Intensive BGAT	Mean Accuracy Index=NR (SEM: NR)		
		Control	Mean Accuracy Index=NR (SEM: NR)		
Cox et al.(122)	1989	BGAT	Mean Accuracy Index=NR (SEM: NR)	Time effect: *P*=NS Group effect: *P*=NS Group * Time interaction: *P*=0.001	Evidence that BGAT awareness training may improve BG estimation accuracy.
		Control	Mean Accuracy Index=NR (SEM: NR)		
Cox et al.(123)	1988	BGAT	Mean Accuracy Index=NR (SEM: NR)	Time effect: *P*=0.037 Group * Time interaction: *P*=0.019	Evidence that BGAT awareness training may improve BG estimation accuracy when compared to a non-specific control group.
		Control	Mean Accuracy Index=NR (SEM: NR)		

AI=accuracy index; BG=blood glucose; BGAT=blood glucose awareness raining; HAATT=hypoglycemia anticipation, awareness and treatment training; NS=between groups comparison not statistically significant; SD=standard deviation; SEM=standard error of mean; SMBG=self-monitoring of blood glucose.

Severe Hypoglycemic Event Rate

As discussed in the previous section, currently available evidence on the effectiveness of BGAT (in all its forms) suggests that it may be effective in improving the ability of some individuals with type 1 diabetes to estimate their blood glucose levels. Limited data suggest that BGAT may also improve blood glucose awareness in some individuals with hypoglycemic unawareness. If these findings are valid, then one would expect that BGAT would reduce the incidence of severe hypoglycemic events among individuals with type 1 diabetes, because such individuals will be more aware of their glycemic status and, when necessary, better able to take corrective action to prevent the occurrence of severe hypoglycemia. The purpose of this subsection is to determine whether there is evidence to support this contention.

Two of the five included studies (that enrolled a total of 107 individuals) reported on the incidence of severe hypoglycemic episodes experienced by individuals with type 1 diabetes following exposure to BGAT when compared with a control. Relevant outcome data from these studies are presented in Table 30. The findings of the two studies are inconsistent. One study observed a significant reduction in the incidence of severe hypoglycemic episodes while the other study did not. Other than noting that the two studies used slightly different versions of BGAT (HAATT and GBAT-1) and pointing out the slight differences in the enrollees in these studies, the inconsistencies in the findings of the two studies could not be satisfactorily explained. Given this, we conclude that, at this time, it remains unclear whether the apparent benefits of an improved ability to estimate blood glucose levels are expressed as measurable reductions in the incidence of severe hypoglycemia in individuals with type 1 diabetes.

Table 30. Effect of BGAT on Incidence of Severe Hypoglycemic Episodes

Reference	Year	Cohort	Severe Hypoglycemic Episodes		Conclusion
			Mean (SD or SEM)	*P*=	
Cox et al.(116)	2004	HAATT	0.4 episodes/person/month	*P*=0.03	Study provides evidence in support of the contention that HAATT reduces the incidence of severe hypoglycemia.
		SMBG	1.7 episodes/person/month		
Kinsley et al.(120)	1999	BGAT	0.69 (SEM: 0.07) episodes/day	NS	No evidence to support contention that BGAT-3 reduces the incidence of hypoglycemia in tightly controlled individuals with type 1 diabetes any more effectively than does a non-specific control.
		Cholesterol Ed.	0.68 (SEM: 0.06) episodes/day		

BGAT=blood glucose awareness training; HAATT= hypoglycemia anticipation, awareness and treatment training; SMBG=self-monitoring of blood glucose.

Section Summary

Our evidence-based conclusions on the effectiveness of BGAT are presented below.

1. **BGAT improves the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels (Strength of Evidence: Moderate)**

   A total of five prospective studies that enrolled a total of 188 individuals with type 1 diabetes evaluated the effectiveness of BGAT in improving the accuracy of self-determined blood glucose estimates. All five studies were controlled; four were randomized and one was non-randomized controlled trials. The overall quality of the evidence base was moderate (Median quality score=6.80; Range: 5.70 to 7.50).

   Qualitative assessment of the available data found that currently available evidence, though not of high quality, consistently demonstrated that BGAT improves the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels.

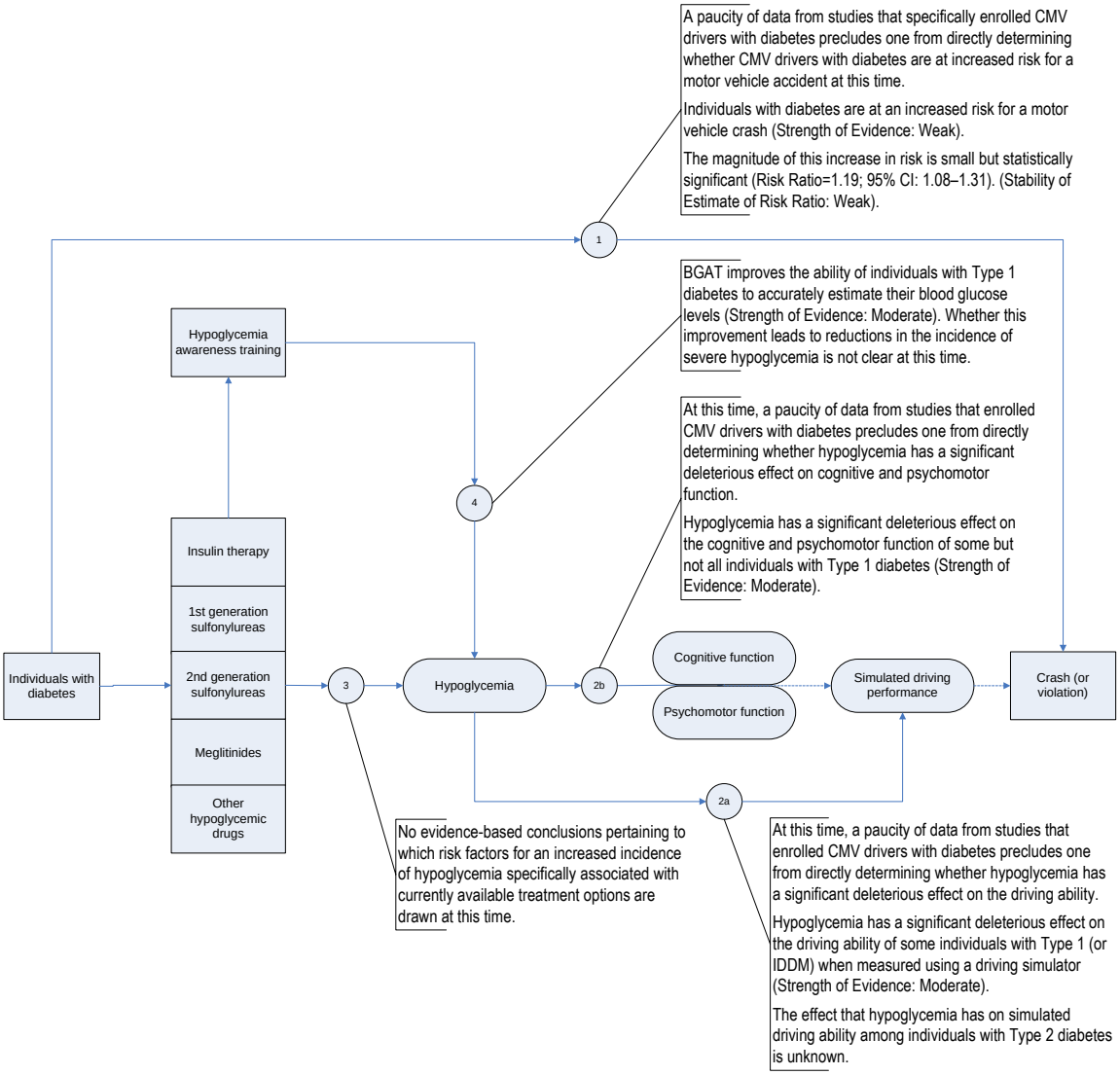
2. **A paucity of consistent evidence precludes a determination from being made concerning whether BGAT is effective in reducing the incidence of severe hypoglycemia.**

   Two moderate-quality studies that enrolled a total of 107 individuals with type 1 diabetes presented data on the incidence of severe hypoglycemia following exposure to BGAT. The results of these two small studies were inconsistent, with one study finding a benefit while the other study did not. The inconsistencies in the findings of the two studies cannot be explained. Given this, it remains unclear whether exposure to BGAT results in measurable reductions in the incidence of severe hypoglycemia among individuals with type 1 diabetes.

Conclusions

The overall findings of the present evidence report are summarized by Figure 15. Direct evidence pertaining to diabetes and CMV driver safety was extremely scarce; only one such study (which addressed Key Question #1) was included in this evidence report. Consequently, we were obliged to turn to evidence from studies that assessed the relationship between diabetes and driver safety in the general population. On average, drivers in the general population differ from CMV drivers in that they are far less experienced. On the other hand, CMV drivers are exposed to far more risk than the average driver by virtue of the fact that they are driving for longer periods of time over far greater distances in a large variety of traffic environments. Whether superior driving experience outweighs the risks associated with increased driving exposure is unclear; however, the fact that truck driving is considered to be a very dangerous occupation suggests that it does not.

Figure 15. Overall Summary of Findings



Our assessment of the available evidence pertaining to crash risk found that the average driver with diabetes (type 1 or type 2) has a small but significant incremental increase in the risk for motor vehicle crash over and above that of a comparable individual who does not have the disorder (Risk Ratio=1.19, 95% CI; 1.08–1.31). In other words, the risk of an individual with diabetes being involved in a motor vehicle crash is approximately 1.19 times greater than that of a comparable individual who does not have the disorder.

One possible cause of the excess risk for a crash seen in individuals with diabetes is incapacitation due to hypoglycemia. Indeed there is ample anecdotal evidence in the literature (in the form of case reports) to suggest that some crashes experienced by individuals with diabetes can be attributed to hypoglycemia. To date no well designed study has provided direct evidence supporting the contention that hypoglycemia is the major contributor to the increased risk for crash among individuals with diabetes. Indirect evidence, however, is reasonably plentiful. Our analysis of data from 13 independent studies consistently found that moderate-to-severe hypoglycemia has a deleterious effect

on the driving ability, cognitive function, and psychomotor function of some individuals with type 1 diabetes. Due to a paucity of acceptable data, we were unable to determine the extent to which hypoglycemia affected these measures in individuals with type 2 diabetes.

Because there is a reasonably large body of literature showing that hypoglycemia occurs more often among individuals treated with insulin than among those treated by pharmacotherapy or diet alone, one would might reasonably expect that insulin-treated drivers are at a higher risk for a motor vehicle crash risk than non-insulin treated drivers. Surprisingly, a series of analyses designed to determine the excess risk associated with insulin treatment did not confirm this. One possible explanation for the finding that drivers with insulin-treated diabetes do not appear to be at a higher risk for a motor vehicle crash than drivers with non-insulin treated diabetes is that a process of self-selection occurs among individuals with insulin-treated diabetes whereby the most severely affected individuals either restrict their driving or do not drive at all. As a consequence, crash risk estimates determined for drivers with insulin-treated diabetes are based on a subset of individuals with lower rates of hypoglycemia than would be seen if all individuals with insulin-treated diabetes drove.

Because there is evidence (albeit indirect) to suggest that hypoglycemia is a primary contributor to the excess crash risk observed among individuals with diabetes, a number of groups have attempted to develop programs that aim to diminish its incidence. One such program is BGAT (Blood Glucose Awareness Training). BGAT is a psychoeducational intervention program designed to assist individuals with type 1 diabetes in managing and maintaining tight diabetic control. The value of BGAT in managing and maintaining control in individuals with type 2 diabetes has not been assessed. Our analysis of studies of the effectiveness of BGAT found that the program was effective in improving the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels. However, currently available evidence has not consistently demonstrated that this improvement in blood glucose level estimation leads to measurable reductions in the incidence of severe hypoglycemia among individuals with type 1 diabetes.

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Appendix A: Search Summary

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across Embase, Medline, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), Emtree, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMedline, Systematic, OldMedline)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Accidents
Accidents, traffic
Accident$.ti.
Collision$.ti.
Crash$.ti.
Highway safety
Motor traffic accidents
Traffic safety
Wreck$.ti.

Blood glucose awareness training
BASH
BGAT$
BINGO
Blood glucose awareness training
Glycemic awareness training
HAATT
Hypoglycemia anticipation awareness and treatment training

Diabetes
Diabet*
Diabetes
Diabetic
Hypoglycaem*
Hypoglycem*
Hypoglycemia.de.

Driving
Automobile driver examination
Automobile driving
Automobiles
Car driving
Driving.ti.
Driving behavior
Motor vehicles

Psychomotor performance
Aware$
Cognition
Mental function
Mental processes
Neuropsychological performance
Perceptual motor processes
Performance
Psychomotor
Psychomotor performance
Reaction time
Response latency
Unaware$

Set Number	Concept	Search statement
1	Diabetes	Diabet$ or exp diabetes/ or exp hypoglycemia/ or hypoglycem$ or hypoglycaem$
2	Accidents	Accidents, traffic.de. or highway safety.de. or motor traffic accidents.de. or traffic accident.de. or traffic safety.de. or crash$.ti. or wreck$.ti. or collision.ti. or accident$.ti.
3	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or driving.ti.
4	Mental function	Exp mental processes/ or exp psychomotor/ or exp neuropsychological performance or exp performance/ or exp reaction time/ or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/
5	Glycemic awareness	Blood glucose awareness training or BGAT or glycemic awareness training or hypoglycemia anticipation awareness and treatment training or HAATT or BINGO or BASH or aware$ or unaware$
6	Combine sets	or/2-5
7	Combine sets	1 and 6
8	Limit by publication type	7 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
9	Limit by study type	8 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)

Appendix B: Retrieval Criteria

Appendix B will list the retrieval criteria for each key question. An example of a small set of retrieval criteria are presented below.

Retrieval Criteria for Key Question 1

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash either directly (risk for a fatal or non-fatal crash) associated with diabetes.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have diabetes.

Retrieval Criteria for Key Question 2

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article may describe a study that attempted to evaluate the relationship between hypoglycemia and the following direct and indirect measures of driver safety:
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function
- Article must describe a study that includes a comparison group comprised of comparable individuals with diabetes who did not have hypoglycemia at the time of testing.

Retrieval Criteria for Key Question 3

- Article must describe a study specifically designed to identify treatment related risk factors for an increased incidence of severe hypoglycemia.
- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Subjects enrolled in study must be representative of the general population of individuals with diabetes who would qualify for a CMV driver's license if current restrictions on insulin use were lifted.
- Treatment (drug or delivery device) must have FDA approval for marketing in the U.S.
- In order to allow reasonable estimates of the incidence of severe hypoglycemia to be determined the followup time of comparative phase of study must be ≥1 year.

- In order to allow reasonable estimates of the incidence of severe hypoglycemia to be determined, each arm of the study must be large enough to detect an incidence rate as low as 0.01 episodes/person year.
- Article must describe a study that attempted to empirically determine the relationship between the risk for a hypoglycemic event and the following factors:
    - Mechanism of glycemic control (insulin, 1st generation[20] sulfonylureas, 2nd generation[21] sulfonylureas, biguanides, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, and other drugs used to control blood glucose levels)
    - Route of insulin administration (inhaled, subcutaneous injection, pump)

Retrieval Criteria for Key Question 4

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to evaluate the effectiveness of hypoglycemia awareness training.
- Article should describe a controlled trial

[20] 1st generation sulfonylureas include: tolbutamide, acetohexamide, tolazamide, chloropropamide.
[21] 2nd generation sulfonylureas include: glipizide, glyburide, glimepiride

Appendix C: Inclusion Criteria

Appendix C will list the inclusion criteria for each key question. An example of a small set of retrieval criteria are presented below.

Inclusion Criteria for Key Question 1

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Article must describe a study that attempted to directly determine the risk for a motor vehicle crash either directly (risk for a fatal or non-fatal crash) associated with diabetes.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have diabetes.
- Article must present motor vehicle crash risk data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 2

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Article may describe a study that attempted to evaluate the relationship between hypoglycemia and the following direct and indirect measures of driver safety:
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function
- Article must describe a study that includes a comparison group comprised of comparable individuals with diabetes who did not have hypoglycemia at time of testing.

Inclusion Criteria for Key Question 3

- Article must describe a study that was specifically designed to identify treatment related risk factors for an increased incidence of severe hypoglycemia.[22]
- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Subjects enrolled in study must be representative of the general population of individuals with diabetes who would qualify for a CMV driver's license if current restrictions on insulin use were lifted.
- Treatment (drug or delivery device) must have FDA approval for marketing in the U.S.
- In order to allow reasonable estimates of the incidence of severe hypoglycemia to be determined the followup time of comparative phase of study must be ≥6 months.
- In order to allow reasonable estimates of the incidence of severe hypoglycemia to be determined, each arm of the study must be large enough to detect an incidence rate as low as 0.01 episodes/person-year.
- Article must describe a study that attempted to empirically determine the relationship between the incidence of severe hypoglycemia and any of the following factors:
    - Mechanism of glycemic control (insulin, 1st generation[23] sulfonylureas, 2nd generation[24] sulfonylureas, biguanides, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, and other drugs used to control blood glucose levels)
    - Route of insulin administration (inhaled, subcutaneous injection, pump)

Inclusion Criteria for Key Question 4

- Article must describe a study that attempted to evaluate the effectiveness of hypoglycemia awareness training.
- Article must describe a study that utilized a control group composed of comparable individuals who did not receive BGAT or,
- Article must describe a study that compared effectiveness of BGAT in groups of individuals who differed from one another in their blood glucose awareness status.

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[22] Studies designed to determine the risk of severe hypoglycemia related to the implementation of intensive insulin therapy are not considered in this evidence report because the association between intensive therapy and an increased incidence of hypoglycemia has been well described.

[23] 1st generation sulfonylureas include: tolbutamide, acetohexamide, tolazamide, chloropropamide.

[24] 2nd generation sulfonylureas include: glipizide, glyburide, glimepiride

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.

Appendix D: Excluded Articles

Table D-1. Excluded studies (Key Question 1)

Reference	Year	Reason for Exclusion
Harsch et al.(124)	2002	Does not address Key Question #1. Does address KQ3
Songer et al.(125)	2002	Does not address Key Question 1. Presents risk factors for crash among individuals with diabetes.
Kennedy et al.(126)	2002	Does not Address Key Question 1. All individuals were involved in an accident that hospitalized the individual for 3 or more days.
Gislason et al.(127)	1997	Does not address Key Question 1. No outcome data relevant to KQ 1 presented that could be assessed.
Sagberg et al.(128)	2006	Method (induced-exposure method) does not allow one to determine crash risk of diabetics when compared to rest of population. OR for crash based on data from 16 diabetics at fault for a crash and 8 diabetics involved in a crash but not at fault. Control group too small.
MacLeod et al.(19)	1993	Does not address Key Question 1.
Mathieson et al.(129)	1997	Does not address Key Question 1. Examines risk of any type of accident. Does not report motor vehicle crash data separately.
Cox et al.(130)	2005	Abstract only
Cox et al.(131)	2004	Abstract only
Dionne et al.(132)	1993	Superseded by more recent article
Diamond et al.(133)	2005	5 selected case reports
Canfield et al.(134)	2000	Does not address Key Question 1. Aircraft crashes
Waller(135)	1965	Does not address Key Question 1. Crash data for individuals with diabetes not presented separately.
Frais et al.(136)	1972	Letter
Christian et al.(137)	1972	Letter
Leyshon et al.(138)	1972	Case report
Santer et al.(139)	1972	Letter
Clarke et al.(140)	1980	Letter
Kernbach-Wighton et al.(141)	2003	Does not address Key Question 1. Hypoglycemia and moving violations
Dionne et al.(142)	1995	Superseded by more recent article

Table D-2. Excluded studies (Key Question 2)

Reference	Year	Reason for Exclusion
Diamond et al.(133)	2005	Study too small-5 case reports
Schultes et al.(143)	2005	Examines effects of hypoglycemia in individuals without diabetes
Zammitt et al.(144)	2005	Abstract
Brody et al.(145)]	2004	Examines effects of hypoglycemia in individuals without diabetes
Cox et al.(89)	2003	Case-control study using evidence base include in Cox et al.(88)
Hermann et al.(146)	2003	No outcome of interest to key question addressed
Schachinger et al.(147)	2003	Examines effects of hypoglycemia in individuals without diabetes
Stork et al.(148)	2003	Abstract
McAulay et al.(149)	2001	Examines effects of hypoglycemia in individuals without diabetes
Owen et al.(150)	2001	Examines effects of hypoglycemia in individuals without diabetes
Evans et al.(151)	2000	Examines effects of hypoglycemia in individuals without diabetes
Fruewald-Schultes et al.(152)	2000	Examines effects of hypoglycemia in individuals without diabetes
McCrimmon et al.(153)	1999	No outcome of interest to key question addressed
McCrimmon et al.(154)	1996	Examines effects of hypoglycemia in individuals without diabetes
Fitten et al.(155)	1995	Not relevant
Gold et al.(156)	1995	Examines effects of hypoglycemia in individuals without diabetes
Blackman et al.(157)	1990	Examines effects of hypoglycemia in individuals without diabetes
Stevens et al.(158)	1989	Examines effects of hypoglycemia in individuals without diabetes
Holmes et al.(159)	1988	Compared groups of diabetics with normal control or poor control. <10 pats. per arm.

Table D-3. Excluded studies (Key Question 3)

Reference	Year	Reason for Exclusion
Cefalu et al.(160)	2001	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Laberge-Nadeau et al.(161)	1998	Abstract
McAuley et al.(162)	2004	Letter
Corsello et al.(163)	1999	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Shorr et al.(164)	1997	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Shapiro et al.(165)	2005	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Allen et al.(166)	2004	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Weinger et al.(167)	2001	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Rosenstock et al.(168)	2004	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Richardson et al.(169)	2005	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Bastyr et al.(170)	2000	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Thamer et al.(171)	1999	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Owen et al.(150)	2001	Not relevant to Key Question 3
Akber et al.(172)	2001	Not designed to determine risk ratio of severe hypoglycemia associated with a diabetes treatment when compared to another treatment or placebo.
Murata et al.(108)	2005	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Donnely et al.(18)	2004	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Pederson-Bjergaard et al.(30)	2004	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Johnson et al.(31)	2002	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Ter Braak et al.(32)	2000	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Muhlhauser et al.(33)	1998	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Bott et al.(34)	1997	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Gold et al.(35)	1997	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Shorr et al.(21)	1997	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Pampanelli et al.(36)	1996	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Bell et al.(37)	1994	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
EURODIAB(110)	1994	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
MacLeod et al.(19)	1993	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration

Reference	Year	Reason for Exclusion
Mulhauser et al.(29)	1991	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Ward et al.(41)	1990	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Casparie & Elving(20)	1985	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Clarke et al.(45)	1980	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Gold et al.(173)	1994	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration
Goldgewicht et al.(111)	1983	Did not provide details of risk factors for hypoglycemia that pertain specifically to a treatment type or mode of administration

Table D-4. Excluded studies (Key Question 4)

Reference	Year	Reason for Exclusion
Fehm-Wolsdorf et al.(174)	2005	Meeting Abstract
Grossman et al.(175)	2005	Case Reports
Nordfeld et al.(176)	2005	Does not address Key Question 4. Not BGAT study
Hernandez et al.(177)	2004	Does not address Key Question 4. Not BGAT study
Nebel et al.(178)	2004	Does not address Key Question 4. Not BGAT study
Braun et al.(179)	2003	Does not address Key Question 4. Not BGAT study
Erskine et al.(180)	2003	Does not address Key Question 4. Not BGAT study
DAFNE Study Group(181)	2002	Does not address Key Question 4. Not BGAT study
Nordfeld et al.(182)	2002	Does not address Key Question 4. Not BGAT study
Cox et al.(183)	2001	No control group
Cox et al.(184)	2001	Meeting Abstract
Snoek et al.(185)	2001	Does not address Key Question 4. Not BGAT study
Tankova et al.(186)	2001	Does not address Key Question 4. Not BGAT study
Bott et al.(187)	2000	Does not address Key Question 4. Not BGAT study
Schiel et al.(188)	1998	Does not address Key Question 4. Not BGAT study
Schiel et al.(189)	1997	Does not address Key Question 4. Not BGAT study
Cox et al.(190)	1995	No control group
Fanelli et al.(191)	1994	Does not address Key Question 4. Not BGAT study
Nurick et al.(192)	1991	Study size too small

Appendix E: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI evidence reports differ substantially from other systematic review in that we provide two types of conclusion; qualitative conclusions and quantitative conclusions. In order to reach these conclusions we use an algorithm developed by ECRI to guide the conduct and interpretation of the analyses performed during the development of this evidence report. The algorithm, which is presented in Figure E-3 through Figure E-6, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately to the stability and strength of evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. Each of these sections, the decision points that fall within them, and the decision rules that were applied at each step in the present evidence report are described below.

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: 1) to assess the quality of each included study; 2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used the ECRI Quality Scale I (for randomized and non-randomized comparative studies), the ECRI Quality Scale III (for pre-post studies) and a revised version of the Newcastle-Ottawa Quality Assessment Scale (for case-control studies).(101) These instruments are presented in Appendix F.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key question specific evidence base into one of three distinct categories; high, moderate or low quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median EQS I Score	Median EQS III Score	Median NOQAS Score
High Quality	≥8.0		
Moderate Quality	6.0 to 7.9	≥9.0	≥8.0
Low Quality	≤6.0	<9.0	<8.0

Note that it is not possible for an evidence base consisting of case-control trials to be categorized as high quality. This is the consequence of the fact that this study design can never be protected from potential bias.

Decision Point 3: Quantitative Analysis Performed?

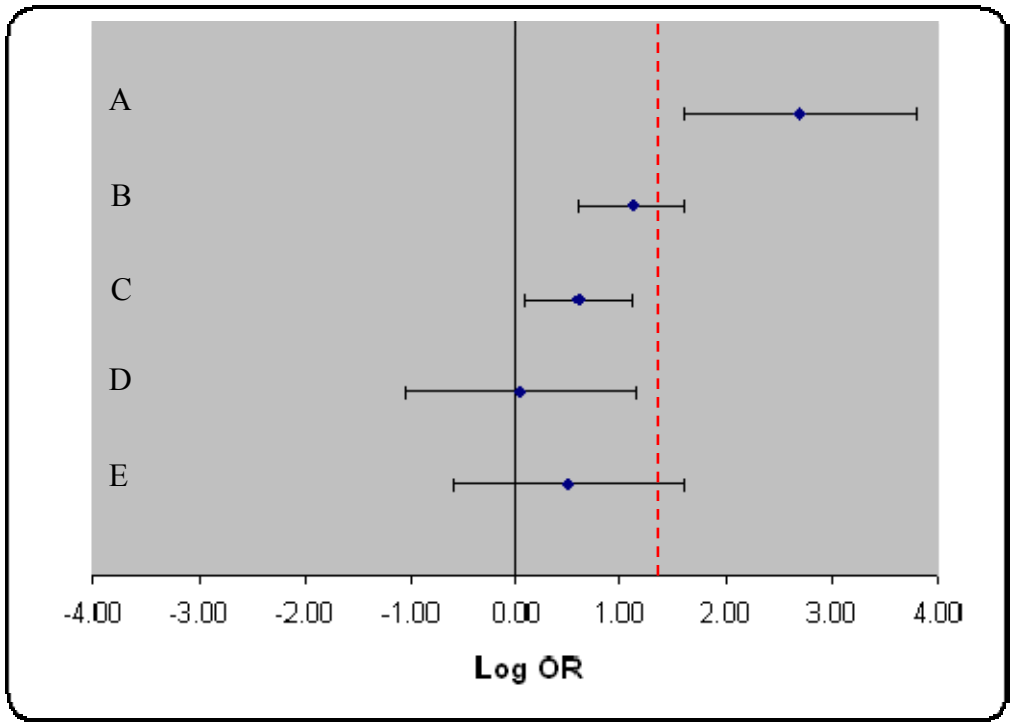
In this evidence report the answer to Decision Point 3 depended on a number of factors; the number of available studies and the adequacy of reporting of study findings. For any given question, combinable data from at least 3 studies must be available before a quantitative analysis will be considered. If 4 or more studies were available but poor reporting precluded ECRI from directly computing relevant effect size estimates for >75% of the available studies, no quantitative analysis were performed. If no quantitative analyses were performed, we moved directly to Decision Point 8 which deals with the assessment of the available evidence with the aim of drawing a purely qualitative conclusion.

Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of homogeneity. For this evidence report we used both the Q-statistic and Higgins and Thompson's I^2 statistic.(7) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50% and $P(Q)$ >0.10.

If the findings of the studies included were homogeneous (I^2 <50% and $P(Q)$ >0.10), we obtained a summary effect size estimate by pooling the results of these studies using fixed-effects meta-analysis (FEMA). Having obtained a summary effect size estimate, we then determined whether this estimate effect size estimate was informative. That is, we determined whether the findings of the meta-analysis allowed a conclusion to be drawn. To see what is meant by this, consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is non-informative.

Figure E-1. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant but it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect and it is also unclear whether the treatment effect is clinically important. This latter finding is thus non-informative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the fixed-effects meta-analysis were found to be informative, we next assessed the stability of the summary effect size estimate obtained. Stability refers to the likelihood that a summary effect estimate will be substantially altered by changing the underlying assumptions of the analysis. Analyses that are used to test the stability of an effect size estimate are known as sensitivity analyses. Clearly, ones confidence in the validity of a treatment effect estimate will be greater if sensitivity analyses fail to significantly alter the summary estimate of treatment effect.

For this evidence report, we utilized four different sensitivity analyses. These sensitivity analyses are:

1. *Random-effects meta-analysis of complete evidence base.* When the quantitative analysis is performed on a subset of available studies, a random-effects meta-

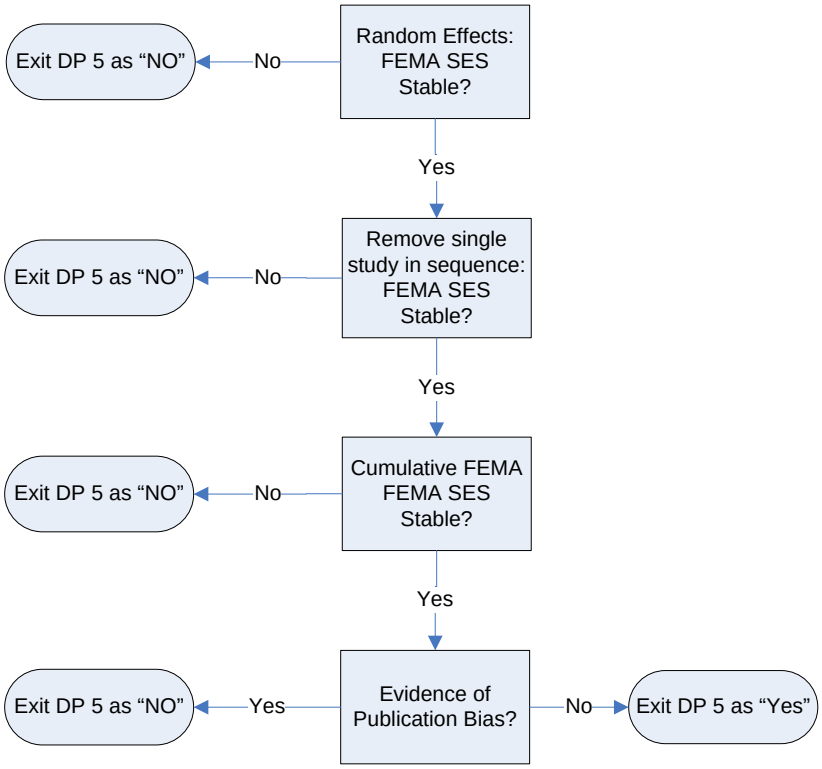
analysis that includes imprecise estimates of treatment effect calculated for all available studies will be performed. For this evidence report, the summary estimate of treatment effect determined by this analysis will be compared to the summary effect size estimate determined by the original fixed-effects meta-analysis. If the random effects effect size estimate differs from the original fixed-effects meta-analysis by >±5%, the original effect size estimate will not be considered stable.

2. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.
3. *Publication bias test.* The publication bias test used in this evidence report was that of Duval and Tweedie.(11-13,73) Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(12,13)estimates the number of unpublished studies (and their effect sizes). After addition of any "missing" data to the original meta-analysis, the overall effect size is estimated again. If evidence of publication bias was identified and the summary effect size estimate, adjusted for "missing" studies, differed from the pooled estimate of treatment effect determined by the original fixed-effects meta-analysis by >±5%, the we determined that the findings of our original analysis are not robust and the effect size estimate is not stable.
4. *Cumulative fixed-effects meta-analysis.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect size estimate. For this evidence report, we performed three different cumulative fixed-effects meta-analyses:
    a. Studies were added in order of weight
    b. Studies were added cumulatively to a fixed-effects meta-analysis by date of publication-oldest study first.
    c. Studies were added cumulatively to a fixed-effects meta-analysis by date-newest study first.

    In each instance, the pooled effect size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect size estimate effect of >±5%.

Because it is possible to reach Decision Point 6 with two different types of evidence base (100% or <100% ≥75% of total available evidence base), two slightly different sets of sensitivity analyses are needed. Figure E-2 shows the procedural algorithm that were used when dealing with these two types of evidence base.

Figure E-2. Sensitivity Analysis Algorithm 1: Used when Original Fixed-Effects Meta-Analysis Utilized Data from All Available Studies



Decision Points 6 and 7: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report we did not encounter any situations where we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 6 and 7 are irrelevant to the present report and we do not discuss them further.

Decision Point 8: Are Qualitative Findings Robust?

Decision Point 8 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. For this evidence report, a single sensitivity analysis was performed–a random-effects cumulative meta-analysis (cREMA). We considered our qualitative findings to be overturned only when the findings of the cREMA altered our qualitative conclusion (i.e., a statistically significant finding became non-significant as studies were added to the evidence base). If the qualitative findings of the last three study additions were in agreement then we concluded that our qualitative findings were robust.

Decision Point 9: Are Data Qualitatively Consistent?

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example one might ask,

"When compared to insulin injection, do all included studies find that inhaled insulin is a significant risk factor for a motor vehicle crash?

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn ones qualitative conclusion.

The algorithm divides the magnitude of effect into two categories–large and not large. Determining the threshold above which the observed magnitude of effect can be considered to be "large" cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect size estimate is "extremely large" using a modified Delphi technique.

Figure E-3. General Section

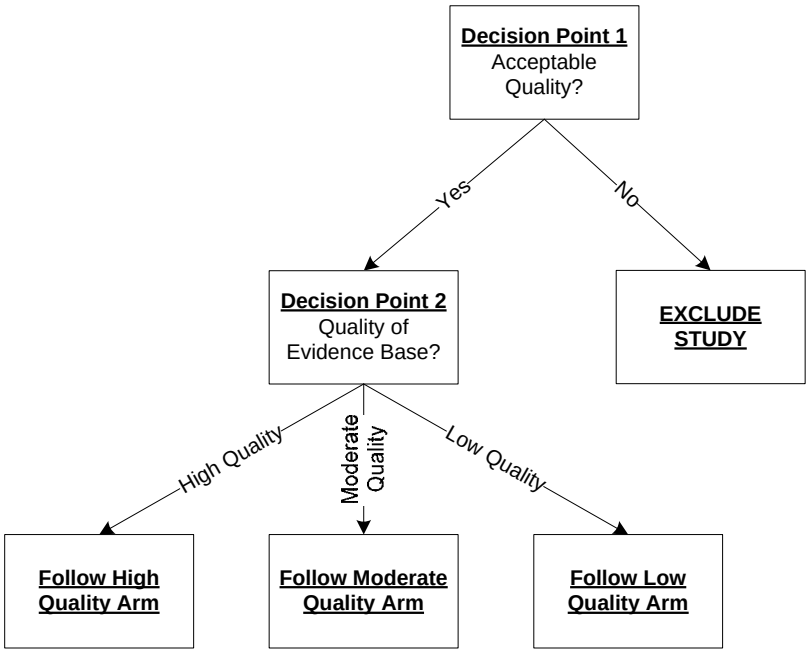


Figure E-4. High Quality Pathway

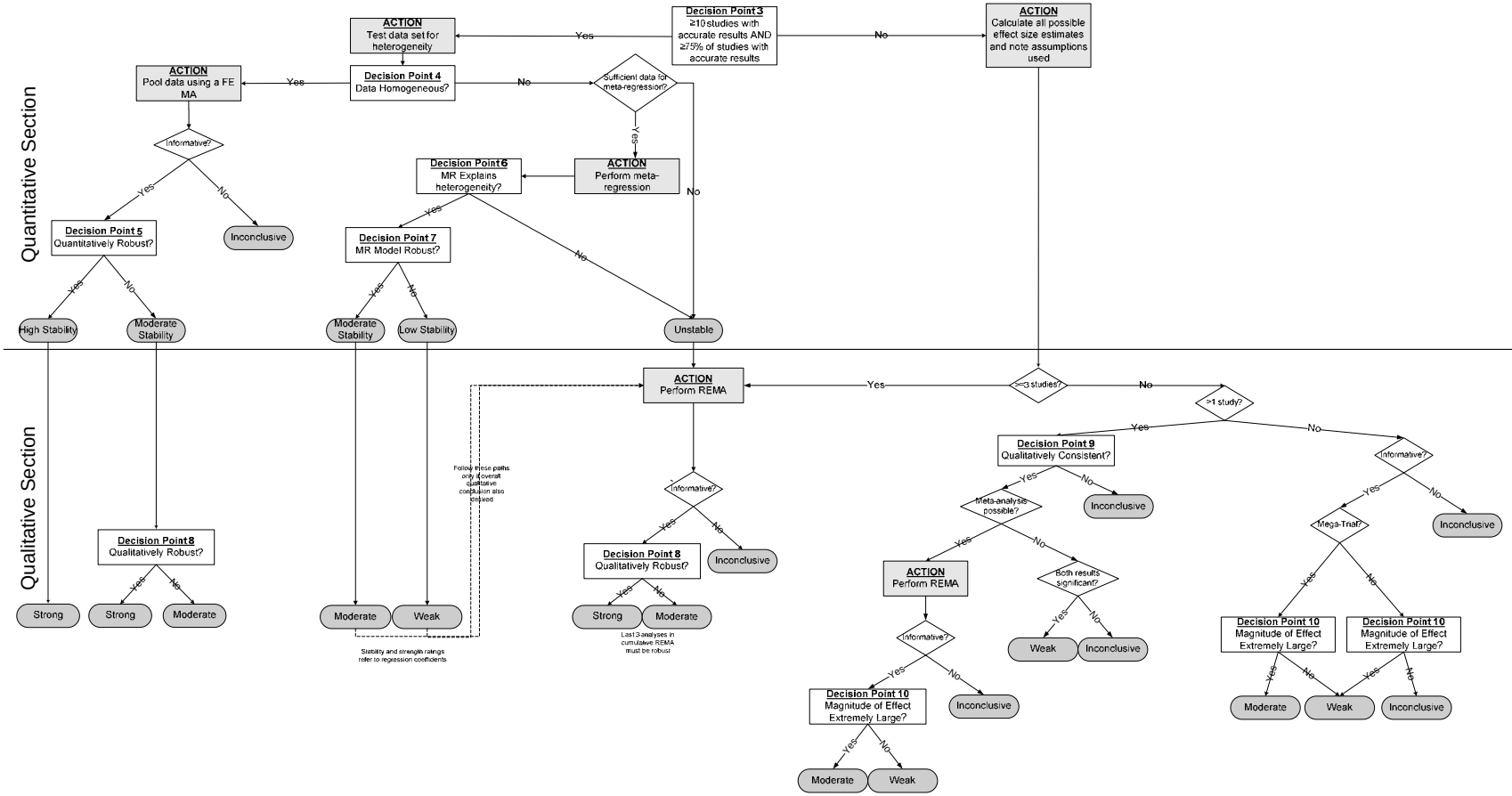


Figure E-5. Moderate Quality Pathway

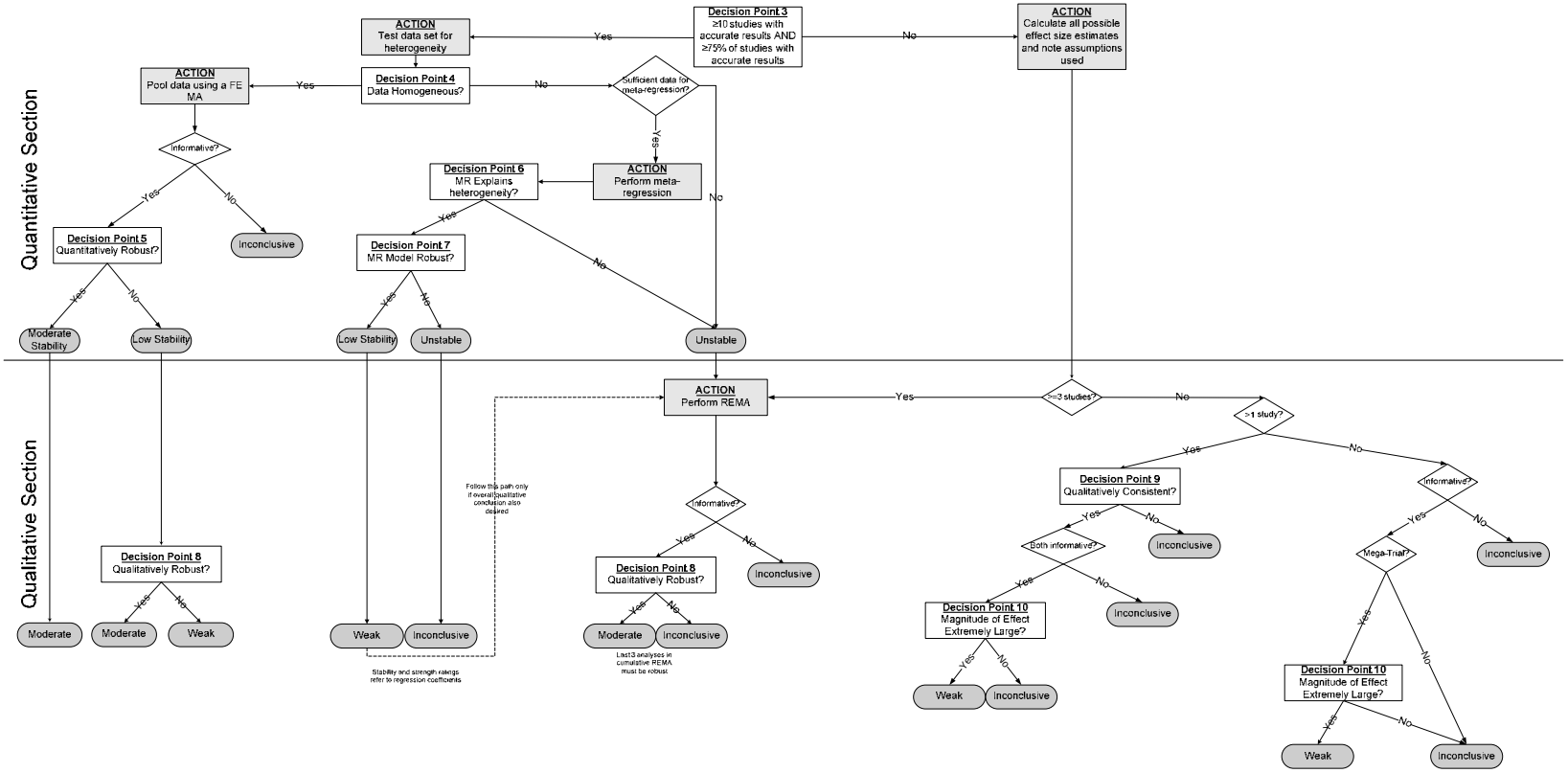
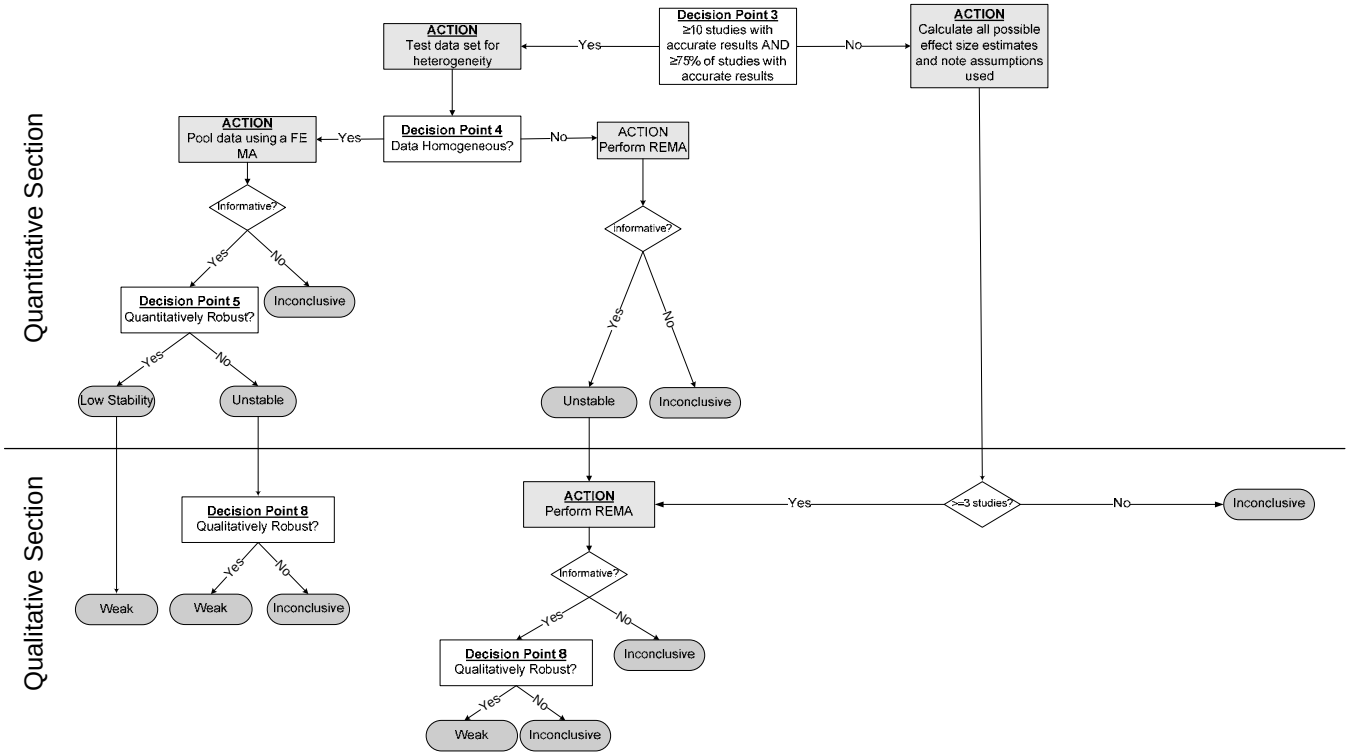


Figure E-6. Low Quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report; ECRI Quality Scale I for comparative trials, ECRI Quality Checklist III for before-after studies, and a revised version of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(101)

ECRI Quality Scale I: Controlled Trials

Domain	Question #	Question
Comparability	1	Were patients randomly assigned to the study's groups?
	2	Did the study employ stochastic randomization?
	3	Were any methods other than randomization used to make the patients in the study's groups comparable?
	4	Were patients assigned to groups based on factors other than patient or physician preference?
	5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
	6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
	7	Was the comparison of interest prospectively planned
	8	Did ≥85% of the patients complete the study?
	9	Was there a ≤15% difference in completion rates in the study's groups?
	10	Were all of the study's groups concurrently treated?
	11	Was compliance with treatment ≥85% in both of the study's groups?
	12	Were all of the study's groups treated at the same center?
Blinding	13	Were subjects blinded to the treatment they received?
	14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
	15	Was the treating physician blinded to the groups to which the patients were assigned?
	16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
	17	Was there concealment of allocation?
Outcomes	18	Was the outcome measure of interest objective **and** was it objectively measured?
	19	Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
	20	Was the instrument used to measure the outcome standard?
Intervention	21	Was the same treatment given to all patients enrolled in the experimental group?
	22	Was the same treatment given to all patients enrolled in the control group
	23	Were the follow-up times in all of the study's relevant groups approximately equal?
Investigator Bias	24	Was the funding for this study derived from a source that does not have a financial interest in its results?
	25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section supported by the data presented in the articles results section?

ECRI Quality Scale III: Pre-Post Studies

Domain	Item	Question
	1	Was the study prospective?
	2	Did the study enroll all patients or consecutive patients?
	3	Were the criteria for including and excluding patients based on objective laboratory and/or clinical findings?
	4	Were the patient inclusion/ exclusion criteria established a priori?
	5	Was the same initial treatment given to all patients enrolled?
	6	Did all patients receive the same subsequent treatment(s)?
	7	Was the outcome measure objective and was it objectively measured?
	8	Did ≥85% of patients complete the study?
	9	Were the characteristics of those who did and did not complete the study compared, and were these characteristics similar?
Investigator Bias	10	Was the funding for this study derived from a source that does not have a financial interest in its results?
	11	Were the author's conclusions, as stated in the abstract or the article's discussion section supported by the data presented in the article's results section?

Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

The original Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies consisted of ten questions. We adapted the instrument to better capture some sources of bias that were not considered in the original 10-item scale.

Domain	Question #	Question
Selection	1	Do the cases have independent validation?
	2	Are the cases representative?
	3	Are the controls derived from the community?
	4	At the designated endpoint of the study, do the controls have the outcome of interest?
Comparability	5	Does the study control for the most important confounder?
	6	Does the study control for any additional confounders?
Exposure/Outcome	7	Was exposure/outcome ascertained through a secure record (surgical, etc.)
	8	Was the investigator who assessed exposure/outcome blinded to group patient assignment?
	9	Was the same method of exposure/outcome ascertainment used for both groups?
	10	Was the non-response rate of both groups the same?
	11	Was the investigation time of the study the same for both groups?
Investigator Bias	12	Was the funding free of financial interest?
	13	Were the conclusions supported by the data?

Appendix G: Study Summary Tables

Study Summary Tables (Key Question 1)

<table>
<tr><td colspan="15">Reference: Laberge-Nadeau C, Dionne G, Ekoe JM, Hamet P, Desjardins D, Messier S, Maag U. Impact of diabetes on crash risks of truck-permit holders and commercial drivers. Diabetes Care 2000 May;23(5):612-7.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">To analyze crash risks for users and non-users if insulin among Class 1-articulated truck (AT) and Class-3-single unit truck (ST) commercial drivers in Quebec, Canada.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case control study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-2</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="12">All diabetic AT and ST CMV permit holders known in 1989</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="12">Women, permit holders, >65 years old (in 1989)</td></tr>
<tr><td colspan="2">Study population Characteristics</td><td colspan="12">The study population contained all diabetic AT and ST permit holders known in 1989. Study population group-matched with a random sample of the same classes of permit holders in good health stratified by 5-year age-groups.</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="12">Good</td></tr>
<tr><td>Methods</td><td colspan="14">Diabetic and healthy non-diabetic truck drivers in Québec were followed to observe their crash rates. Personal driving records of Québec truck-permit holders linked with their health records and a survey on driving risk exposure. Data on permits (e.g., age, sex, and driving class), medical conditions, and crashes in the province of Québec for individuals extracted from administrative files of Société de l'Assurance Automobile du Québec (SAAQ). SAAQ has access to driver records, including all crashes from police reports. Since 1989, every truck-permit holder in Quebec must submit medical reports from physicians and eye specialists to SAAQ. The SAAQ may designate a specialized physician for such reports. For validation, health status data also obtained for 96.5% of the study subjects from Régie de l'Assurance Maladie du Québec (RAMQ). Data rendered anonymous by SAAQ and RAMQ. Exposure to driving measured through a 1990–1991 telephone survey of all truck-permit holders, carried out by a polling firm. SAAQ, RAMQ, and the polling firm files linked.

Survey asked about driving patterns, including kilometers driven per year, and proxies for exposure to crash risk, such as working radius, type of road, and time of day, for year before the interview. Crash experience analyzed for all permit holders (without risk-exposure variables) and professional drivers (i.e., drivers with an AT or ST permit who drove a vehicle at work such as a truck, van, or car). For this second group, authors used risk exposure variables.

Health status defined by combining the following: 1) medical and treatment codes from the SAAQ, 2) ICD-9 codes for diagnoses, 3) codes for medical acts from the RAMQ. Control population permit holders coded by SAAQ as having either good health or no medical evaluation and no health problems noted in RAMQ files. Whether individuals with diabetes treated by diet, oral hypoglycemic agents, or insulin recorded. Co-morbid conditions also considered, resulting in 3 categories of diabetic drivers: 1) insulin users (73% without comorbidity, 20% with visual, and 7% with cardiovascular problems), 2) nonusers of insulin without complications (no comorbidity, 64% treated with oral agents), and 3) nonusers with complications (hypertension, cardiovascular, or visual, 62% treated with oral agents).

Authors used permit holder–years as units of observation for analysis. Unit of observation defined using crash records and attributes of permit holder during 1 calendar year. Driving risk-exposure variables obtained for 1990 taken as constant for 4 years, provided driving experience confirmed by respondent.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Mean yearly crash rates per driver with diabetes compared with controls using age and both quantitative and qualitative measures of driving exposure as co-variables. Medical status introduced as a nested factor within permit class. Negative binomial regression models for panels with entries and exits estimated using log-linear specification. Logarithm of individual number of crashes per year regressed on a vector of explanatory variables for the ith individual. Crashes considered as rare and independent events. Only 1.3% had >1 crash in a year. Binomial models used to account for individual heterogeneity unexplained by available co-variables. Regression coefficients tested with Wald statistic. RR of means for individuals belonging to a particular group versus a comparison group estimated. RR gives marginal effect of belonging to a particular group in terms of relative crash risks, all other variables being equal.

Two separate sets of analysis performed. First on all drivers. Second on only those with risk exposure data. Models without driving exposure data contained only the observation period, age group, and health status as variables. Models with driving exposure data controlled for the distance driven, type of road, driving time, etc.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td rowspan="2">Score = 9.4</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes</td><td colspan="14">Crash Relative Risk (95% CI)</td></tr>
</table>

Assessed					
Results	**Explanatory variable**	**n**	**Mean**	**RR**	**95% CI**
	Class AT				
	Good health	5,813	0.14	1.00	Reference category
	Diabetes without complications	1,253	0.15	1.14	0.94–1.38
	Diabetes with complications	1,227	0.14	1.17	0.96–1.43
	Diabetes treated with insulin	640	0.13	1.02	0.78–1.33
	Class ST				
	Good health	3,145	0.12	1.00	Reference category
	Diabetes without complications	472	0.19	**1.68***	**1.27–2.24**
	Diabetes with complications	435	0.11	1.03	0.73–1.46
	Diabetes treated with insulin	468	0.12	1.07	0.77–1.47
	Class AT†				
	Good health	1,736	0.17	1.00	Reference category
	Diabetes without complications	369	0.13	0.81	0.58–1.14
	Diabetes with complications	299	0.15	0.87	0.61–1.25
	Diabetes treated with insulin	121	0.11	0.65	0.35–1.21
	Class ST†				
	Good health	795	0.14	1.00	Reference category
	Diabetes without complications	127	0.24	**1.76***	**1.06–2.91**
	Diabetes with complications	84	0.13	0.96	0.48–1.91
	Diabetes treated with insulin	62	0.16	1.02	0.48–2.17
Authors' Comments	Authors note that their finding of an increased crash risk for commercial drivers with uncomplicated diabetes not using insulin is a new finding. The authors suggest that the lack of consistent increases in crash risk among diabetic commercial drivers with complications or who use insulin may be a "healthy worker effect" that masks the real underlying crash risk, because these licensees have a lower participation rate as professional drivers.				
Reviewers' Comments	Moderate quality study. Exposure controlled for. Results indicate that at least some commercial vehicle drivers (ST permit holders who are not taking insulin and who do not have diabetic complications) are at increased risk for a motor vehicle accident when compared to comparable group of healthy commercial drivers.				

* Statistically significantly greater than non-diabetic reference standard (P <0.05)

† With risk exposure controlled for

<table>
<tr><td colspan="15">Reference: McGwin G Jr, Sims RV, Pulley L, Roseman JM. Diabetes and automobile crashes in the elderly. A population-based case-control study. Diabetes Care 1999 Feb;22(2):220-7.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="2">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="6">4</td></tr>
<tr><td colspan="2">✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="6"></td></tr>
<tr><td>Research Question</td><td colspan="14">To estimate the association between diabetes and its complications and at-fault injurious automobile crashes among older drivers.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case-control study.</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-2</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="13">Age: ≥65 years; In possession of a valid driver's license between 1991 and 1996; agreement to participate in study.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">See Table G-1.
<u>Cases</u> were individuals who lived in Mobile County, Alabama involved in at least one automobile crash between Jan 1st 1991 and Dec 31st 1996. Police records corresponding to the crashes incurred by 447 obtained from the Alabama Department of Public Safety (DPS). Records examined to determine whether the case subject could have been at least partially at fault in the crash. Of the 447 crash-involved drivers, 249 (56.0%) found to be at least partially at fault.
<u>Controls</u> were individuals 454 (74.1%) non-crash involved drivers.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Standard demographic information (age, sex, race, marital status, education), information on diabetes, other chronic medical conditions, medications, driving habits, and visual function collected by telephone interview. Interviews conducted by trained interviewers blind to case status. (Table G-2)
Subjects who reported having diabetes queried about disease duration, severity (e.g., frequency of hyperglycemic/hypoglycemic episodes), treatment (e.g., diet, oral hypoglycemic agents, insulin), and symptoms (e.g., dizziness, frequent urination). Subjects asked whether a physician, nurse, or other health care professional had told them they had, or were receiving treatment for, any of the following: cataracts, arthritis, cancer, detached retina, memory problems, hearing problems, heart disease, epilepsy, glaucoma, high blood pressure, kidney disease, Parkinson's disease, and stroke. Subjects asked whether they had been diagnosed with any other conditions not explicitly mentioned and whether they were taking any other medications.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Frequency distributions calculated for demographics, driving exposure, diabetes, and other health conditions for crash-involved and non–crash-involved subjects. For demographic and driving variables, crude odds ratios (ORs) and 95% CIs computed. For chronic medical conditions, analyses performed with and without adjustments for demographic factors and annual mileage. For diabetes characteristics, ORs and 95% CIs calculated and adjusted for demographic factors and annual mileage, and for demographic factors, annual mileage, and chronic medical conditions.
Analyses conducted using unconditional logistic regression comparing at-fault crash-involved subjects (case subjects) with non–crash-involved subjects (control subjects). Relationship between diabetes characteristics and subgroups of crash-involved drivers (at-fault and not-at-fault) assessed.</td></tr>
<tr><td rowspan="4"></td><td rowspan="2">Quality Score = 10</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Risk of at-fault crash (expressed as Odds Ratio's)(see Table G-3)
Risk of not at fault crash (not considered here)</td></tr>
<tr><td>Results</td><td colspan="14">See Table G-2 and Table G-3</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">No evidence of an overall association between diabetes and at-fault crash involvement observed. No evidence of an association between at-fault crash and treatment type observed. Study investigators note that there was an increased injurious crash risk associated with diabetes in subjects who had been involved in an automobile crash in the previous 4 years.</td></tr>
<tr><td>Reviewers' Comments</td><td colspan="14">Well designed case control trial.</td></tr>
</table>

NR=Not reported; OR=Odds ratio

Table G-1. Demographic and Driving Characteristics of Included Drivers

	At-fault crash-involved drivers (%)	Non–crash-involved drivers		Not-at-fault crash-involved drivers	
		%	OR (95% CI)	%	OR (95% CI)
n	249	454		198	
Age (years)					
65–68	21.3	25.7	1.0 (referent)	39.6	1.0 (referent)
69–72	25.4	24.4	1.3 (0.8–2.0)	23.6	2.0 (1.2–3.4)
73–77	25.8	25.7	1.2 (0.8–1.9)	23.6	2.0 (1.2–3.4)
78–93	27.5	24.2	1.4 (0.9–2.1)	13.2	3.9 (2.1–7.0)
P for trend		0.21		0.001	
Sex					
Male	49.6	49.1	1.0 (referent)	51.1	1.0 (referent)
Female	50.4	51.0	1.0 (0.7–1.3)	48.9	1.1 (0.7–1.6)
Race					
White	74.6	80.0	1.0 (referent)	74.2	1.0 (referent)
Black	23.0	16.8	1.5 (1.0–2.1)	22.5	1.0 (0.6–1.6)
Other	2.5	3.2	0.8 (0.3–2.2)	3.3	0.7 (0.2–2.4)
Quality of driving					
Excellent/good	82.7	86.8	1.0 (referent)	89.9	1.0 (referent)
Average/fair/poor	17.3	13.2	1.4 (0.9–2.1)	10.1	1.9 (1.0–3.4)
Annual mileage					
<4,000	25.8	35.2	1.0 (referent)	32.4	1.0 (referent)
4,000–7,999	26.2	21.5	1.7 (1.1–2.5)	22.0	1.5 (0.9–2.5)
8,000–13,000	21.3	22.1	1.3 (0.8–2.0)	21.4	1.2 (0.7–2.2)
>13,000	26.6	21.3	1.7 (1.1–2.6)	24.2	1.4 (0.8–2.3)
P for trend		0.07		0.48	
Prior crash involvement					
No	63.9	79.0	1.0 (referent)	66.5	1.0 (referent)
Yes	36.1	21.1	2.1 (1.5–3.0)	33.5	1.1 (0.8–1.7)

Table G-2. Medical and Visual Function Characteristics of Enrolled Drivers

	At-fault crash-involved drivers (%)	Not-at-fault crash-involved drivers			Non–crash-involved drivers		
		%	OR (95% CI)	OR (95% CI)*	%	OR (95% CI)	OR (95% CI)*
n	249	198			454		
High blood pressure	42.9	45.7	0.9 (0.6–1.3)	0.9 (0.6–1.4)	45.7	0.9 (0.6–1.2)	0.9 (0.6–1.3)
Stroke	7.3	6.9	1.1 (0.5–2.3)	1.1 (0.5–2.4)	4.1	1.8 (0.9–3.7)	1.9 (0.9–3.9)
Heart disease	26.0	24.3	1.1 (0.7–1.7)	1.0 (0.7–1.7)	20.2	1.4 (0.9–2.0)	1.5 (1.0–2.2)
Cataracts	44.6	35.1	1.5 (1.0–2.2)	1.1 (0.7–1.8)	42.8	1.1 (0.8–1.5)	1.0 (0.7–1.5)
Glaucoma	6.9	5.2	1.4 (0.6–3.2)	1.0 (0.4–2.5)	8.9	0.8 (0.4–1.4)	0.7 (0.4–1.3)
Kidney disease	3.2	6.4	0.5 (0.2–1.2)	0.4 (0.2–1.2)	4.7	0.7 (0.3–1.6)	0.7 (0.3–1.6)
Near vision score ≤75%	13.2	8.0	1.8 (0.9–3.4)	1.6 (0.8–3.3)	12.3	1.1 (0.7–2.0)	1.0 (0.6–1.7)
Far vision score ≤75%	41.0	36.0	1.2 (0.8–1.9)	1.1 (0.7–1.7)	36.5	1.2 (0.9–1.7)	1.2 (0.8–1.7)
Peripheral vision score ≤75%	8.5	4.7	1.9 (0.8–4.5)	1.6 (0.7–3.9)	6.0	1.5 (0.8–2.7)	1.4 (0.8–3.0)

Lower vision scores represent greater impairment. For all ORs, the reference is those without condition. For vision variables, the reference category is those with scores >75%. *The second set of ORs for each group has been adjusted for age, sex, race, and annual mileage.

Table G-3. Crude and Adjusted ORs and 95% CIs for Association between Diabetes Characteristics and At-Fault Crash Involvement

	At-fault crash-involved drivers (%)	Not-at-fault crash-involved drivers				Non–crash-involved drivers			
		%	OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡	%	OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡
n	249		198				454		
No diabetes	86.5	84.1	1.0 (referent)	1.0 (referent)	1.0 (referent)	86.1	1.0 (referent)	1.0 (referent)	1.0 (referent)
Diabetes	13.6	16.0	0.8 (0.5–1.4)	0.9 (0.5–1.5)	0.7 (0.4–1.3)	14.0	1.0 (0.6–1.5)	0.9 (0.6–1.5)	1.1 (0.7–1.9)
Diet control only	1.2	1.7	0.9 (0.5–1.5)	0.7 (0.1–3.4)	0.6 (0.1–3.5)	2.5	0.5 (0.1–1.7)	0.5 (0.1–1.8)	0.6 (0.2–2.5)
Pharmacological control	12.3	14.3	0.7 (0.1–3.7)	0.9 (0.5–1.7)	0.7 (0.4–1.4)	11.4	1.1 (0.7–1.8)	1.1 (0.7–1.7)	1.3 (0.7–2.2)
Diet control only	1.2	1.7	0.7 (0.1–3.7)	0.7 (0.1–3.4)	0.6 (0.1–3.5)	2.5	0.5 (0.1–1.8)	0.5 (0.1–1.8)	0.6 (0.2–2.5)
OHAs	8.2	8.8	0.9 (0.5–1.8)	1.0 (0.5–1.9)	0.7 (0.3–1.5)	5.9	1.4 (0.8–2.5)	1.3 (0.7–2.4)	1.3 (0.7–2.6)
Insulin	4.1	5.5	0.9 (0.4–2.1)	0.9 (0.4–2.3)	0.9 (0.4–2.5)	5.5	0.9 (0.4–1.8)	0.9 (0.4–1.8)	1.3 (0.6–2.9)
Diabetic retinopathy	1.6	1.1	1.5 (0.3–8.2)	1.9 (0.3–10.9)	1.8 (0.3–10.4)	1.5	1.1 (0.3–3.8)	1.4 (0.3–4.0)	1.3 (0.3–5.2)
Diabetic neuropathy	1.2	0.5	2.3 (0.2–21.8)	2.8 (0.3–28.3)	§	0.6	2.0 (0.4–9.8)	2.6 (0.5–13.1)	2.2 (0.4–11.2)

ORs given are *crude ORs, †adjusted for age, sex, race, and annual mileage, or ‡adjusted for age, sex, race, annual mileage, chronic medical conditions, and visual function. §Undefined.

<table>
<tr><td colspan="15">Reference: Gresset J, Meyer F. Risk of automobile accidents among elderly drivers with impairments or chronic diseases. Can J Public Health 1994 Jul-Aug;85(4):282-5.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="4">2</td><td colspan="4">3</td><td colspan="5">4</td></tr>
<tr><td>✓</td><td colspan="4"></td><td colspan="4"></td><td colspan="5"></td></tr>
<tr><td>Research Question</td><td colspan="14">To determine the risk for a motor vehicle crash associated with chronic medical impairments including diabetes among men in their 70th year in Quebec, Canada.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case-control study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-2</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="13">Male; 70 years old</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Female; not in 70th year of life.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">Cases: Age: all had a motor vehicle crash (registered by Societe de l'Assurance Automobile du Quebec [SAAQ]) during their 70th year; males only; passenger vehicle permit holders.
Controls: Randomly selected from 30,000 male drivers who had not had a motor vehicle crash during their 70th year.
(Table G-4)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Poor</td></tr>
<tr><td>Methods</td><td colspan="14">All cases were identified from a listing of persons who had had a motor vehicle crash (registered by Societe de l'Assurance Automobile du Quebec [SAAQ]) during their 70th year in 1988 or 1989. All controls were randomly selected from 30,000 male drivers who had not had a motor vehicle crash during their 70th year. Records from these individuals were obtained from the SAAQ.
Questionnaires were mailed to study subjects asking information on mileage and prevailing driving conditions.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Multiple logistic regression was used to obtain OR to estimate RR and CI.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score = 7.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>NR</td><td>Y</td><td>NR</td><td>Y</td></tr>
<tr><td rowspan="2">Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Risk of crash (expressed as Odds Ratios) (Table G-5)</td></tr>
<tr><td>Results</td><td colspan="14">See Table G-4 and Table G-5</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">Drivers with impairments or chronic medical conditions are not at increased risk of road accidents.</td></tr>
</table>

*Adjusted for demerit points, mileage, number of hours driving, frequency of driving during rush hour

Table G-4. Prevalence of Chronic Impairments and Diseases among 1400 cases and 2,636 Controls

	Cases		Controls	
	N	%	N	%
Visual Impairments	118	8.4	209	7.9
Minimal VA	52	3.7	99	3.8
Monocularity	5	0.4	10	0.4
Minimal VA Monocularity	61	4.4	100	3.5
Other Impairments	120	8.6	228	8.7
Hearing Impairments	57	4.1	119	4.5
Amputations	13	0.9	29	1.1
Paralyses	50	3.6	80	3.0
Heart Diseases	448	32.0	820	31.1
Hypertension	176	12.6	346	13.1
Heart Failure	18	1.3	36	1.4
Arrhythmias	30	2.1	35	1.3
Ischemic heart disease	121	18.6	442	16.8
Diabetes mellitus	260	8.6	226	8.6
Non-IDDM	103	7.4	196	7.4
IDDM	18	1.3	30	1.1

Table G-5. Odds Ratios of Accidents and related 95% CI for Chronic Impairments and Diseases among 70 year old Drivers

	Odds Ratio	95% CI	
Visual Impairments	1.07	0.84	1.36
Minimal VA	0.99	0.71	1.40
Monocularity	0.95	0.32	2.77
Minimal VA Monocularity	1.16	0.83	1.60
Other Impairments	0.99	0.78	1.26
Hearing Impairments	0.90	0.65	1.24
Amputations	0.84	0.44	1.67
Paralyses	1.18	0.89	1.70
Heart Diseases	1.04	0.91	1.20
Hypertension	0.95	0.78	1.16
Heart Failure	0.94	0.53	1.66
Arrhythmias	1.63	1.00	2.65
Ischemic heart disease	1.13	0.96	1.34
Diabetes mellitus	1.01	0.80	1.27
Non-IDDM	0.99	0.77	1.27
IDDM	1.13	0.63	2.04

Reference: de Klerk NH, Armstrong BK. Admission to hospital for road trauma in patients with diabetes mellitus. J Epidemiology Community Health 1993 Sep;37(3):232-7.														
Key Questions Addressed	**1**		**2**		**3**		**4**							
	✓													
Research Question	Whether diabetics demonstrate a detectable increase in risk of having a road crash.													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	People born before 1965 with any mention of DM on their hospital discharge abstract in the years 1971 – 1979. People in Western Australia admitted to hospital with road trauma.												
	Exclusion Criteria	For DM patients, road crash could not be external cause of identifying hospital admission. Earliest admission did not terminate with death in hospital.												
	Study population Characteristics	N=8623 patients with DM												
	Generalizability to CMV drivers													
Methods	Public Health Department of Western Australia records for people born before 1965 with any mention of DM on their hospital discharge abstract in the years 1971 – 1979 were collected. Public Health Department of Western Australia records for people in Western Australia admitted to hospital with road trauma were collected. Records were compared to provide a list of all people admitted to hospital for road trauma who were also listed on the discharge abstract as having DM. The diabetic group was then compared to mortality records from Western Australia to determine the date and cause of death of any of the diabetics who had died before 31 Dec 1979.													
Statistical Methods	Numerators for rate calculations were determined by counting the numbers of admissions for road trauma (road crash as external cause) or death linked to the diabetic group after the earliest admission for DM. Denominators were derived from the aggregate of person years accumulated by the diabetics from discharge after their earliest admission until death or 31 Dec. 1979, whichever was earlier.													
Quality assessment	**Quality Score = 6.3**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	N	Y	N	N	Y	N	Y	Y	N	Y	Y
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	Risk of crash (expressed as Rate Ratios)(Table G-6;Table G-7)													
Results	See Table G-6 and Table G-7.													
Authors' Comments	The findings suggest that there is an increased risk of admission to hospital in young (<55 years of age) men with diabetes in charge of a vehicle.													

Table G-6. Observed and expected number of hospital admissions after road crashes in patients with diabetes mellitus

Age	Men				Women			
	Obs	Exp	Obs/Exp	95% CI	Obs	Exp	Obs/Exp	95% CI
15-24	11	7.7	1.43	0.72-2.56	0	3.1	0	----
25-34	9	3.9	1.79	0.72-3.69	5	1.9	2.63	0.85-6.14
35-44	5	3.6	1.39	0.45-3.25	3	2.0	1.50	0.31-4.39
45-54	13	6.0	2.17	1.15-3.71	4	3.2	1.25	0.34-3.20
55-64	2	7.8	0.26	0.30-0.94	7	5.6	1.25	0.50-2.58
65-74	8	9.1	0.88	0.28-1.73	4	8.1	0.49	0.13-1.25
>75	1	5.4	0.19	0.05-1.06	2	5.8	0.34	0.04-1.23
Total	47	43.5	1.08	0.79-1.44	25	29.6	0.84	0.54-1.24

Table G-7. Observed and expected number of hospital admissions after road crashes in patients with diabetes mellitus according to the patient's road use status at the time

Road Use Status	Observation	Men			Women		
		15-54 years	>55 years	All ages	15-54 years	>55 years	All ages
Vehicle Driver	Obs	17	5	22	2	3	5
	Exp	6.1	6.5	12.6	2.3	2.9	5.2
	Obs/Exp	2.79†	0.77	1.75	0.87	1.03	0.96
Motor and Pedal Cyclists	Obs	6	1	7	1	0	1
	Exp	3.9	1.4	5.3	0.4	0.2	0.6
	Obs/Exp	1.54	0.71	1.32	2.5	0	1.67
Vehicle Passenger	Obs	0	1	1	5	3	8
	Exp	2.5	2.2	4.7	2.9	6.0	8.9
	Obs/Exp	0	0.43	0.21	1.72	0.50	0.90
Pedestrian	Obs	7	0	7	1	3	4
	Exp	1.5	6.0	7.5	0.7	5.1	5.8
	Obs/Exp	4.67†	0	0.93	1.43	0.59	0.69
Unspecified	Obs	6	4	10	3	4	7
	Exp	7.2	6.2	13.4	3.8	5.2	9.0
	Obs/Exp	0.83	0.65	0.75	0.79	0.77	0.78
Total	Obs	36	11	47	12	13	25
	Exp	21.2	22.3	43.5	10.1	19.4	29.5
	Obs/Exp	1.70†	0.49*	1.08	1.19	0.67	0.85

† Obs/Exp ratio significantly different from 1.0, p <0.01.

* Obs/Exp ratio significantly different from 1.0, p <0.05

‡ Probability of observing 0 events from a Poisson distribution of mean 6 is less than 0.01

<table>
<tr><td colspan="15">Reference: Cox DJ, Penberthy JK, Zrebiec J, Weinger K, Aikens JE, Frier B, Stetson B, DeGroot M, Trief P, Schaechinger H, Hermanns N, Gonder-Frederick L, Clarke W. Diabetes and Driving Mishaps. Diabetes Care 2003;26(8):2329-2334.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="7">4</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="7"></td></tr>
<tr><td>Research Question</td><td colspan="14">Goals of study were as follows: 1) to assess the relative impact of diabetes and its treatment on driving mishaps, 2) to assess how often the more unrefined measures of automobile crashes and moving vehicle violations occur relative to hypoglycemic stupor while driving and the need for assistance with hypoglycemia while driving, and 3) to identify factors predictive of driving mishaps.</td></tr>
<tr><td>Study Design</td><td colspan="14">Multicenter (11 centers) Cross-sectional retrospective study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-2</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Type I diabetes; type II diabetes; Non-diabetic spouse of individual with type I or type II diabetes</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Absence of drivers license; Insulin or oral agent treatment initiated in two years prior to study.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">See Table G-8.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Patients and spouses were asked to complete and return a one-page questionnaire containing the following questions as dependent variables:
1. How many automobile accidents did you have in the last 2 years?
2. How many times were you cited for a moving vehicle violation by a police officer in the last 2 years?
3. How many times in the last 2 years has someone had to help you drive because of hypoglycemia?
4. How many times in the last 2 years have you driven in a hypoglycemia stupor?
5. How many times in the past 6 months have you driven while you were experiencing hypoglycemia symptoms (mild hypoglycemia, not a stupor)?
6. How many miles/kilometers do you routinely drive a year?
7. Has your doctor ever discussed with you hypoglycemia and driving (yes/no)?
8. Is there a blood glucose level at which you would not drive (yes/no)? If yes, what level?
9. How often do you test your blood glucose before you start driving (always/frequently/seldom/never)?</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Control was provided by having similar number of people recruited from each site.
Percentage of individuals with driving mishaps in each group were subjected to X_2 tests to compare differences in frequency distributions across the three groups.
Mann Whitney (Z) test were used for group contrasts.
Discriminant analysis used to compare average crashes per driver by identifying drivers with type I diabetes who had a crash versus drivers with type I diabetes who did not report a crash in the previous 2 years.
Because miles driven and sex did not differ between groups and did not correlate with number of crashes and because previous studies have shown no difference in crash rates between men and women in this age group (12), these variables were not covaried in the analyses. Having a similar number of each group recruited from each site provided the control for location. Given that some drivers with diabetes and multiple motor vehicle crashes and/or episodes of hypoglycemic stupors had substantially reduced their driving (e.g.,100 miles in the past year), we could not use the traditional crashes/100,000 miles driven because of excessive variance. We took a more conservative approach, investigating the percentage of individuals with driving mishaps in each group. To compare average crashes per driver in Europe and the United States, discriminant analysis was used to identify drivers with type 1 diabetes who did versus did not report crashes in the previous 2 years.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality score=8.5</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Difference in frequency of motor vehicle accidents</td></tr>
<tr><td>Results</td><td colspan="14">See Table G-8.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">Driving mishaps (crashes, violations, stupor, receiving assistance, and severe hypoglycemia) are more common among drivers with type I diabetes.
Incidence of driving mishaps was not increased in drivers with type II diabetes compared to controls.</td></tr>
</table>

Table G-8. Demographic characteristics and driving mishaps for US and European drivers with diabetes and nondiabetic spouses

	U.S.	Europe	Total	Probability for group effect*	Probability for location effect*
Descriptive characteristics					
n					
Type 1 diabetic subjects	172	141	313		
Type 2 diabetic subjects	177	97	274		
Nondiabetic spouse control subjects	188	138	326		
Mean age (years)					
Type 1 diabetic subjects	42.4	42.4	42.4	<0.001	NS
Type 2 diabetic subjects	55.8	58.1	56.7		
Nondiabetic spouse control subjects	52.6	48.0	50.6		
Diabetes duration (years)					
Type 1 diabetic subjects	21.6	17.5	19.7	<0.001	<0.01
Type 2 diabetic subjects	11.4	11.2	11.3		
Nondiabetic spouse control subjects	—	—	—		
Female sex (%)					
Type 1 diabetic subjects	55	41	49	0.05	<0.001
Type 2 diabetic subjects	47	24	39		
Nondiabetic spouse control subjects	46	41	43		
Drivers talked to their physicians about driving (%)					
Type 1 diabetic subjects	52	52	52	<0.001	NS
Type 2 diabetic subjects	24	34	27		
Nondiabetic spouse control subjects	—	—	—		
Miles/year					
Type 1 diabetic subjects	12,485	9,969	11,310	NS	<0.001
Type 2 diabetic subjects	13,283	10,999	12,463		
Nondiabetic spouse control subjects	13,674	7,102	10,878		
Frequency of events					
Drivers with crashes (%)					
Type 1 diabetic subjects	16	23	19	<0.001	<0.005
Type 2 diabetic subjects	8	19	12		
Nondiabetic spouse control subjects	6	11	8		
Drivers with violations (%)					
Type 1 diabetic subjects	19	10	15	0.03	0.05
Type 2 diabetic subjects	7	9	8		
Nondiabetic spouse control subjects	13	7	10		
Drivers with hypoglycemic stupor (%)					
Type 1 diabetic subjects	31	4	18	<0.001	<0.001
Type 2 diabetic subjects	8	0	5		
Nondiabetic spouse control subjects	—	—	—		
Drivers who needed assistance (%)					
Type 1 diabetic subjects	24	7	17	<0.001	<0.001
Type 2 diabetic subjects	7	0	5		
Nondiabetic spouse control subjects	—	—	—		
Drivers with hypoglycemia while driving in past 6 months (%)					
Type 1 diabetic subjects	28	16	22	<0.001	<0.001
Type 2 diabetic subjects	6	0	4		
Nondiabetic spouse control subjects	—	—	—		

*Continuous variables (age, diabetes duration, miles) were compared using ANOVA. All other comparisons used nonparametric tests.

Ysander L. Diabetic motor-vehicle drivers without driving-license restrictions. Acta Chir Scand Suppl 1970;409:45-53.														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	Goals of study were as follows: *1*) to assess the relative impact of diabetes on driving mishaps *2*) to determine the proportion of these diabetics who cease driving a car or other motor vehicle on account of the disease or its complications													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Diabetics treated at the Departments of Medicine I and II at the Sahlgrens Hospital in Gothenburg, Sweden Unrestricted driver's license												
	Exclusion Criteria	Restricted driver's license No case record at Sahlgrens Hospital												
	Study population Characteristics	Male: 92% Female: 8% (None in age group 26-30, 1 in age group >60) Average period for possession of a driving license was 23 years in the investigation series. Average period for possession of a driving license during the investigation period 1955-63 was 9.3 years. Average period for possession of a driving license as a diabetic was 7.3 years. Mean observation time for cases *and* controls: 6.0 years. See also Table G-9 and Table G-10.													
	Generalizability to CMV drivers	Unclear												
Methods	Case records of diabetics with unrestricted licenses retrieved from in-patient and out-patient records dated 1961-1963 were obtained. Controls records to create a series of drivers with no known disease who were identical with the investigation series with respect to sex, age, and driving-license period were obtained from the driving-license register at the county administrative board, Gothenburg. A questionnaire was sent to 91% of cases and 90% of controls. The remaining 9% of cases and 10% of controls could not be contacted to receive the questionnaire.													
Statistical Methods	Percentages were calculated for accidents by group.(Table G-11)													
Quality assessment	Quality Score=8.08	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	N	Y	Y	Y	Y	NR	Y	Y	NR	Y	Y
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													
Results	See Table G-11 and Table G-12.													
Authors' Comments	Authors report that there was a reduction in the frequency of road accidents after the onset of diabetes compared with the frequency during the whole ten year period. No accidents occurred that were directly related to diabetes or its treatment. A large proportion of the investigated diabetic drivers (21%) stated that they had ceased to drive a car or other motor vehicle on account of the disease or its complications. Diabetes does not constitute an increased traffic risk. Awareness of the disease appears to be a good prophylactic factor from the road-safety point of view in the higher age groups.													
Reviewers' Comments	Details on driving exposure not obtained from all individuals in study. It is thus unclear whether exposure was adequately controlled for.													

Table G-9. Percentage distribution of the drivers in the investigation series by different age groups

	Age						
	18-20	21-25	26-30	31-40	41-50	51-60	>60
Diabetes Drivers without license restrictions	2%	4%	3%	15%	21%	30%	25%

Percentages are given to the nearest whole number

Table G-10. Percentage distribution of the drivers in the investigation series by different types of treatment and occurrence of retinopathy

	Treatment			Occurrence of Retinopathy
Diabetes Drivers without license restrictions	48%	23%	29%	14%

Percentages are given to the nearest whole number

Table G-11. Percentage distribution of the drivers with road accidents and road accidents and/or serious traffic offenses in the investigation series both during the whole of the 10-year investigation period and after the onset of the disease, and in the control series

	Drivers with Accidents	Drivers without Accidents and/or Serious Traffic Offenses
Investigation series during whole 10 year period *Mean Obs. Period: 9.3* *Number of Drivers: 219*	5.9%	16.9%
Investigation series after onset of disease *Mean Obs. Period: 6.0* *Number of Drivers: 219*	3.7%	119%
Control series *Mean Obs. Period: 6.0* *Number of Drivers: 219*	6.4%	12.3%

Table G-12. Percentage distribution of the drivers who supplied information on annual distance driven, type of driving and place of driving in the investigation series, and the control series

	Investigation Series (n=123)	Control Series (n=161)
Stated Annual Distance Driven		
0-4999	17%	17%
5000-9999	32%	30%
10,000-19,999	29%	41%
20,000 and above	22%	12%
Place of Driving		
Mainly urban areas	85%	70%
Mainly rural areas	15%	30%
Type of Driving		
Mainly for work	58%	57%
Mainly for pleasure	42%	43%

Percentages are given to the nearest whole number.

n=Number of drivers supplying information

Reference: Crancer A Jr., McMurray L. Accident and Violation Rates of Washington's Medically Restricted Drivers. JAMA July 29, 1968: 205 (5)272-76.														
Key Questions Addressed	1		2			3			4					
	✓													
Research Question	Comparison of traffic accident and violation rates of Washington's 39,242 restricted drivers to traffic accident and violation rates of all 1.6 million licensed Washington drivers.													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Driver's license												
	Exclusion Criteria	Not reported												
	Study population Characteristics	Males and Females 13 to >66 years of age.												
	Generalizability to CMV drivers	Unclear												
Methods	Driving records of restricted drivers were collected for the time period 1 Jan 1961 to 1 Oct 1967. Driving records for 1.6 million Washington driving residents collected – no time period specified.													
Statistical Methods	Number of accumulated accidents and violations was determined for the restricted driver group. Number of accidents and violations per restricted driver summarized to obtain totals for all drivers of each sex in each of eight restriction groupings. Accident and violation rates per 100 drivers were computed and compared to accident and violation rates for 1.6 million Washington driving residents.													
Quality assessment	Quality Score = 4.2	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	N	N	N	N	N	Y	Y	N	NR	NR
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													

Results	**Group**	**Accident Rate per 100 drivers**	
	Diabetic restricted drivers (overall)	31.45 (Observed)	26.5 (Population)
	Aged:	**Average per 100**	
	13-17	13.43	N=67 Accidents
	18-20	45.16	N= 248 Accidents
	21-25	51.14	N=436 Accidents
	26-30	40.43	N=329 Accidents
	31-35	29.39	N=347 Accidents
	36-50	31.93	N=1,982 Accidents
	51-65	29.65	N=2,576 Accidents
	66 & older	25.79	N=1,659 Accidents
	Total	31.45	N=7,646 Accidents

Authors' Comments	There were statistically higher accident rates reported for persons whose licenses were restricted due to diabetes, epilepsy, fainting, and other conditions.

Reference: Waller J. Chronic Medical Conditions and Traffic Safety. NEJM Dec 23, 1965: 273 (26)1413-20														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	Comparison of medical and driving records of individuals with chronic medical conditions reported to the California Department of Motor Vehicles with the driving records of individuals not known to have chronic medical conditions.													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Chronic Disease Group: Driving record under review by the California Department of Motor Vehicles												
	Exclusion Criteria	Not reported												
	Study population Characteristics	Mean age: 42.1												
	Generalizability to CMV drivers	Unclear												
Methods	Driving records of chronic medical condition drivers under review by the California Department of Motor Vehicles. Driving records for 922 California drivers collected for single day 3 June 1963. Information gathered for both groups: age, sex, marital status, occupation, number of miles driven annually, three-year accident and violation record. Additional information gathered for medical review group: records of interviews with driver-improvement analysts, medical reports, and information on the nature, duration and severity of medical condition and source, reason and result of each report to the Department about the person.													
Statistical Methods	Sample of driving records for 922 CA weighted to represent the prevalence of drivers in the study group with each license type. Observed vs. Expected Rates compared.													
Quality assessment	Quality= 7.10	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	NR	Y
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													
Results	Group: Diabetics Per 11.1 million miles driven Expected Three-Year Accident Rate: 8.7 Observed Three-Year Accident Rate: 15.5													
Authors' Comments	There were higher accident rates among drivers with medical conditions. Drivers with diabetes, epilepsy, cardiovascular, alcoholism, and mental illness averaged twice as many accidents per 1,000,000 miles of driving.													
Reviewers' Comments	Characteristics of drivers poorly reported.													

Reference: Davis TG, Wehling EH, Carpenter RL. Oklahoma's Medically Restricted Drivers A Study of Selected Medical Conditions. Oklahoma State Medical Association Journal July 1973: (6)322-27														
Key Questions Addressed	1		2			3		4						
	✓													
Research Question	Comparison of medical and driving records of individuals with chronic medical conditions reported to the Oklahoma Department of Public Safety with the driving records of individuals not known to have chronic medical conditions.													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Chronic Disease Group: Driving license granted after review by the Oklahoma Department of Public Safety in 1969. Had to have the following chronic disease(s): diabetes, cardiac or circulatory conditions, epilepsy, or neurological disorder such as stroke or chronic brain syndrome.												
	Exclusion Criteria	Medically restricted drivers whose licenses were revoked or suspended for all or part of 1970.												
	Study population Characteristics	Chronic Disease Group N=318 Males: 69.8% >65 years of age: 20% 25-64 years of age: 37% ≤24 years of age: 43% Control Group N=1,651,245 Males: 54.2% Age: NR												
	Generalizability to CMV drivers	Unclear												
Methods	Driving records of chronic medical condition drivers granted license by review by the Oklahoma Department of Public Safety. Driving records for 1,651,245 Oklahoma drivers collected for 1970. Information gathered for both groups: age, sex, medi cal condition, referral source, and one-year accident and violation record.													
Statistical Methods	Accident percentages and rates compared.													
Quality assessment	Quality Score=5.77	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	N	N	Y	N	Y	N	Y	NR	NR
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Frequency of motor vehicle accidents													
Results	**Group**	**Male**			**Female**			**All**						
	Diabetes	9.2 accidents/100 drivers			4.7 accidents/100 drivers			7.4 accidents/100 drivers						
	General population	8.7 accidents/100 drivers			4.8 accidents/100 drivers			7.1 accidents/100 drivers						
Authors' Comments	There were higher accident rates among diabetic male drivers compared to the control group. There were lower accident rates among diabetic female drivers compared to the control group.													
Reviewers' Comments	Author's conclusions overstate the size of the observed effects.													

Reference: Ysander L. The Safety of Drivers with Chronic Disease. British Journal of Industrial Medicine 1966: (23)28-36														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	To determine the extent to which a drivers disease or the therapy directed against it is to be held responsible for causing a road accident, and to determine whether drivers with chronic disease are over-represented in road accidents.													
Study Design	Matched case-control study													
USPSTF Level														
Population	**Inclusion Criteria**	Driver's license registered with the administrative board of the county of Goteborg and Bohus up through 31 Dec 1961.												
	Exclusion Criteria	Deceased drivers registered with the administrative board of the county of Goteborg and Bohus up through 31 Dec 1961.												
	Study population Characteristics	N=253; Males: 81%; Insulin dependant: 89.72%; Pharmacotherapy: 7.40%; diet: 2.8%												
	Generalizability to CMV drivers	Unclear												
Methods	Driving records of chronic medical condition drivers granted license by review by the driving license registry of Goteborg and Bohus, Sweden Driving records for 195,000 Goteborg and Bohus drivers collected for 1961. Questionnaire about driving exposure, including number of kilometers driven annually, whether driving was urban or rural, and during day or night was administered to medical condition drivers. Control group matched by age, sex, and driving exposure to observation group.													
Statistical Methods	Accident percentages and rates compared.													
Quality assessment	Quality score = 7.12	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	NR	Y
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													
Results	**Diabetics:** 5.0% had road accidents (4 cases-definite connection between the drivers disease and the accident or offense). **Control:** 7.7% had road accidents													
Authors' Comments	There were lower accident rates among diabetic drivers compared to the control group.													

Reference: Campbell EO, Ellis KG. Chronic Medical Conditions and Traffic Violations and Accident Experience of Diabetic Drivers. Modern Medicine November 1969: 24(11)29-31														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	To provide information on the actual incidence of disease-related factors contributing to crashes.													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Diabetes cases in the province of Prince Edward Island, Canada (cases) Drivers licensed in P.E.I. between 1 Jan 1963 and 30 Jun 1968 (controls).												
	Exclusion Criteria	NR												
	Study population Characteristics	Poorly reported. Not possible to determine key characteristics of individuals included in study												
	Generalizability to CMV drivers	Unclear												
Methods	Driving records of diabetes cases registered with the Diabetic Aid Society in the province of Prince Edward Island, Canada. Drivers licensed in P.E.I. between 1 Jan 1963 and 30 Jun 1968. Control group matched by age.													
Statistical Methods	Accident percentages and rates compared.													
Quality assessment	Quality Score=6.54	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	N	N	Y	N	Y	NR	Y	NR	Y
	Low quality	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													
Results	Relative risk for crash greater in individuals with diabetes (RR=1.72).													
Authors' Comments	Actual association of disease-related episodes with the incidents in question could not be established due to data inadequacies.													

Reference: Hanssotia P., Broste SK. The Effect of Epilepsy or Diabetes Mellitus on the Risk of Automobile Accidents. NEJM January 3 1991: 324(1)														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	To systematically compare accident rates among normal subjects with those of subjects with diabetes or epilepsy.													
Study Design	Retrospective cohort study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	All drivers aged 16 to 90 licensed in the seven contiguous zip codes surrounding and including Marshfield, WI.												
	Exclusion Criteria	NR												
	Study population Characteristics	Diabetics N=895 Controls N=30,420 See Table G-13 and Table G-14.												
	Generalizability to CMV drivers	Unclear												
Methods	Medical records of diabetes cases abstracted from the Marshfield Clinic and St. Joseph's Hospital, Marshfield medical care records using ICD-9 codes. Demographic and medical data on disease severity, treatment, and complications abstracted from patient charts by a trained abstractionist and checked by a researcher. Licensing and accident records for all persons who held a regular noncommercial drivers license during the study period and lived in the study area were provided by the Wisconsin Department of Transportation. Diabetics were matched with their driving records. Controls comprised all subjects who did not have an ICD-9 code which suggested diabetes.													
Statistical Methods	Mishap rates per 1,000 years of licensed driving and rate ratios were used to characterize the driving experience of each cohort and its comparison group, according to age. Indirect standardization was used for age due to differences in rates of mishaps and age distribution of affected and unaffected drivers. Standardized mishap ratio (summary ratio) was calculated for each affected cohort and type of mishap. Significance (p value) was used, along with chi-square test with one degree of freedom.													
Quality assessment	Quality score=5.39	1	2	3	4	5	6	7	8	9	10	11	12	13
		N	Y	Y	Y	N	N	N	N	NY	Y	Y	Y	Y
	Low Quality	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents(Table G-15;Table G-16)													
Results	Reported standard mishap ratio (cases:controls): 1.32 (P=0.01) See also Table G-15 and Table G-16.													
Authors' Comments	Study demonstrated increased age-adjusted rates of accidents among drivers with diabetes.													

Table G-13. Characteristics of the Study Cohorts and of All Licensed Drivers in the Area Studied, from 1985-1988

Characteristic	Diabetes Cohort	Epilepsy Cohort	Licensed Drivers*
No. of subjects	484	241	30,420
As of January 1, 1985			
Mean age (yr)	59.0	43.4	38.2
Male sex (%)	57.2	57.7	51.9
Mean years since disease onset†	8.7	11.2	—
During study period (% of subjects)			
Physician recommended no driving†	0.2	11.8	—
Treated primarily in Marshfield†	92.3	92.5	—
Seen at clinic at least once†	99.0	95.9	—

*No data were abstracted for entries for which a dash is shown.
†Data were abstracted from medical records.

Table G-14. Characteristics of the Diabetic Cohort

Characteristic	No. Studied	No. (%) with Characteristic
Diabetes		
Type I	484	48 (9.9)
Type II	484	436 (90.1)
Insulin use*	476	181 (38.0)
≥2 injections/day	179	65 (36.3)
Blood glucose self-test	175	166 (94.9)
≥1 severe reaction†	176	17 (9.7)
Use of oral medication*	473	236 (49.9)
With insulin	236	52 (22.0)
Blood glucose self-test	232	164 (70.7)
≥1 severe reaction†	233	7 (3.0)
Other conditions		
Cardiovascular disease	467	169 (36.2)
Neuropathy	466	90 (19.3)
Retinopathy	466	74 (15.9)
Amputation	465	7 (1.5)
Alcohol abuse	465	14 (3.0)
Epilepsy	484	4 (0.8)

*Patients may have used both insulin and oral medication.
†During the study period.

Table G-15. Accident Rates in the Diabetic and Non-Diabetic Cohorts According to Age

Age (Yr)	Diabetic Cohort			Nondiabetic Cohort			Estimated Rate Ratio
	No. of Person-Years	No. of Accidents	Rate	No. of Person-Years	No. of Accidents	Rate	
<25	65.2	3	46.03	26,657.9	2177	81.66	0.56
25–34	81.2	6	73.87	27,145.3	1326	48.85	1.51
35–44	136.2	9	66.08	18,500.9	830	44.86	1.47
45–54	306.1	14	45.73	11,620.0	456	39.24	1.17
55–64	502.1	24	47.80	10,515.1	336	31.95	1.50
≥65	717.7	32	44.59	10,625.3	340	32.00	1.39
Total	*1808.5*	*88*	*48.66*	*105,064.5*	*5465*	*52.02*	*0.94*
After indirect standardization for age	—	—	68.91	—	—	52.02	1.32

Standardized mishap ratio = 1.32 (95 percent confidence interval, 1.06 to 1.63)
P = 0.0097 (chi-square test)

*Rates shown are accident rates among drivers per 1000 person-years.

Table G-16. Standardized Mishap Ratios (SMR) for Specific Types of Mishaps, According to Study Cohort

Type of Mishap	Diabetes		Epilepsy	
	SMR	95% CI	SMR	95% CI*
Moving violations				
Any	1.14	0.92–1.39	1.13	0.90–1.41
Speeding	1.05	0.80–1.37	0.80	0.57–1.09
Careless driving	1.38	0.97–1.91	1.57†	1.05–2.25
Involving alcohol or drugs	0.66	0.13–1.94	2.75‡	1.50–4.62
Accidents				
Causing injury	1.57†	1.04–2.29	1.63†	0.95–2.60
Causing property damage	1.24	0.95–1.59	1.23	0.86–1.69

*CI denotes confidence interval.
†P<0.05 vs. comparison cohort.
‡P<0.001 vs. comparison cohort.

Reference: Eadington DW, Frier BM. Type 1 Diabetes and Driving Experience: an Eight-year Cohort Study. Diabetic Medicine 1989 (6):137-141														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	To determine whether the original diabetic cohort's driving habits had changed since 1979, to examine the factors which made the diabetic drivers cease driving, and to assess the frequency and causes of road traffic accidents in this group.													
Study Design	Cohort study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Type 1 Diabetes Mellitus. Participant in 1979 study of driving and T1DM in Edinburgh, Scotland												
	Exclusion Criteria	NR												
	Study population Characteristics	Original N=250 8 year followup N=187 (11 male, 7 female untraceable; 37 male, 8 female deceased) No longer driving: 16 male, 8 female Holding HGV license: 3 Lost HGV license since developing diabetes: 5 Refused HGV license since developing diabetes : 8													
	Generalizability to CMV drivers	Unclear												
Methods	Case records of the original 250 T1DM study participants were examined to identify deceased participants, and to document the frequency of diabetic complications among the survivors. Eighteen of original cohort of 250 could not be traced. 45 of the original cohort of 250 had died. Of remaining 187, 166 returned their questionnaire. Causes of death were determined from hospital records, death certificates, and from participants' general practitioners. Surviving participants completed a questionnaire to provide information about current driving practices, including declaration of diabetes to the Driver and Vehicle Licensing Center and to motor insurance companies, whether the declaration had affected insurance premiums, the mileage driven in the previous year, and the need to have a driving license for employment including details of present or past Heavy Goods Vehicle (HGV) licenses. Further information was requested regarding frequency, severity, and intensity of warning symptoms of hypoglycemia in the preceding six months, and whether capillary BG was regularly measured before driving. Occurrence of road traffic accidents during the previous eight years was requested, along with their possible relationship to hypoglycemic episodes.													
Statistical Methods	Statistical comparisons between groups were obtained by Chi-squared tests with Yates correction.													
Quality assessment	Quality Score=7.69	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	NR	NR	Y	NR	Y	Y	Y	NR	Y
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													
Results	Twenty-four participants were no longer driving. Thirty-nine male and seventeen female drivers still held a standard unrestricted drivers license. Three participants were currently holding HGV licenses, five had lost existing HGV licenses since developing diabetes, and eight had been refused new HGV licenses because of diabetes. Twenty-five men and nine women admitted to one or more episodes of hypoglycemia while driving during the eight year study period. Most episodes were mild and self-treated. Seven patients had required external assistance while driving. Three participants no longer drove (two for financial reasons, one due to road traffic accident attributed to hypoglycemia). Twenty nine male drivers admitted to a total of 40 road traffic accidents during the eight year study period, and nine accidents were attributed by the patients to hypoglycemia. Ten female drivers admitted to 15 accidents, none of which were apparently caused by hypoglycemia. The mileage adjusted accident rate for men was 4.9 per million miles, and for women was 6.3 per million miles, for an overall rate of 5.4 per million miles. Department of Transportation statistics on road traffic accidents provides an accident rate for the general population of 10.0 accidents per million miles driven, while analysis of motor insurance claims gives an accident rate of 9.5 accidents per million miles													
Authors' Comments	Self-regulation by diabetic drivers who cease driving because of declining health and driving skills may offset the potential increase in risk of road traffic accidents from hypoglycemia, and may explain why the accident rate was no different from that of a comparable group of non-diabetic drivers.													

Reference: Koepsell TD, Wolf ME, McCloskey L, Buchner DL, Louie D, Wagner EH, Thompson RS. Medical Conditions and Motor Vehicle Collision Injuries in Older Adults. Journal of the American Geriatric Society July 1994 42 (7):695-700														
Key Questions Addressed	1		2			3			4					
	✓													
Research Question	To determine whether medical conditions that can impair sensory, cognitive, or motor function increase the risk of injury due to motor vehicle collision in older drivers.													
Study Design	Matched Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Member of the Group Health Cooperative of Puget Sound (GHC), Washington (cases and controls). ≤ 65 years of age												
	Exclusion Criteria	NR												
	Study population Characteristics	Cases n=234 Controls n=446 See Table G-17.												
	Generalizability to CMV drivers	Unclear												
Methods	Cases had received medical care within 7 days for injuries sustained in a motor vehicle collision in which they were driving one of the vehicles involved. Controls randomly selected from eligible GHC enrollees who had not been injured in a police-reported motor vehicle collision during the calender year of their assigned reference date. Controls matched 2-1 with cases by age, gender, and county of residence. Information about study subjects came from GHC medical records and questionnaires completed by participants. Questionnaire detailed driving habits, number of miles driven per year, health habits, and SES characteristics.													
Statistical Methods	Comparative analysis performed using OR to estimate relative risk. Mantel-Haenszel techniques used for stratified data. Conditional logistic regression.													
Quality assessment	Quality score=9.4	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents.													
Results	DM affected 11.1% of cases and 4.5% of controls, for an OR of 2.6 (95% CI: 1.4-4.7), especially those treated with insulin (OR 5.8, CI 1.2-28.7), or oral hypoglycemia agents (OR 3.1, CI 0.9-11.0), and those with diabetes over 5 years (OR 3.9, CI 1.7 – 8.7).													
Authors' Comments	The older driver with diabetes is at high risk for motor vehicle collision injury.													
Reviewers' Comments	Study of the difference in the prevalence of diabetes (and other disorders) among a population of individuals who crashed (cases) and a population of individuals who did not crash.													

Table G-17. Demographics and Driving Characteristics among Cases and Controls

Characteristics	Cases		Controls	
	n	%	n	%
Age				
65–69	90	38	174	39
70–74	66	28	129	29
75–79	49	21	87	20
80+	29	12	56	13
Sex				
Male	117	50	224	50
Female	118	50	224	50
Race				
White	215	92	432	97
Black	19	8	14	3
Miles driven in previous year				
<5,000	102	44	196	44
5,000–10,000	59	25	125	28
10,000–15,000	46	20	84	19
>15,000	27	12	39	8

Reference: Songer TJ, LaPorte RE, Dorman JS, Orchard TJ, Cruickshanks KJ, Becker DJ, Drash AL. Motor Vehicle Accidents and IDDM. Diabetes Care October 1988 11 (9):701-07														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	To evaluate the risk of motor vehicle accidents among drivers with IDDM.													
Study Design	Sibling matched Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	Individuals enrolled in the Children's Hospital of Pittsburgh IDDM registry diagnosed between 1950 and 1964. Age >17 at IDDM diagnosis Discharge from the hospital on insulin therapy Having received medical care at Children's Hospital at diagnosis or within 1 year of diagnosis. 21 years of age by November 1984 and have a living nondiabetic sibling of the same sex and age ± 5 years. Sibling control ≥21 years of age.												
	Exclusion Criteria	NR												
	Study population Characteristics	See Table G-18 for complete details												
	Generalizability to CMV drivers	Unclear												
Methods	Questionnaire completed driving habits, number of miles driven per year, health habits, SES characteristics and frequency of motor vehicle accidents. (Table G-19)													
Statistical Methods	Matched pair analyses employed McNemer's test, the paired t test, and Wilcoxin's matched pairs signed-ranks test were used to evaluate univariate distances, overall and sex specific, between cases and controls. Unpaired analysis including unpaired t tests and Mann Whitney U test were conducted within each age, marital, and mileage stratum to allow for inclusion of all accident data. Nonparametric analyses completed on the accident and accident per 1,000,000 miles driven data. Multiple logistic regression analysis conducted to simultaneously evaluate the independent associations of diabetes status, age, sex, marital status, and mileage driven and the interactive contribution of diabetes and sex to accident prevalence. In the multivariate analysis, the matching case-control was broken.													
Quality assessment	Quality Score=7.9	1	2	3	4	5	6	7	8	9	10	11	12	13
		N	Y	Y	Y	Y	Y	N	NR	Y	Y	Y	Y	Y
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents (Table G-20;Table G-21;Table G-22)													
Results	IDDM was significantly associated with differences in driving capability among respondents. Multivariate analysis demonstrated that the overall accident risk of the cases and control did not significantly differ. Female drivers with insulin-treated diabetes demonstrated a marked increased risk for motor vehicle accidents (5 times higher, P <.05). Age and marital status were also significantly associated with accident probability in the multivariate model. Traditional risk factors for auto accidents (age and marital status) had an equally strong influence on accident occurrence.													
Authors' Comments	There is little evidence regarding the motor vehicle accident risk of the driver with IDDM. The reason for the excess risk for females is unclear. More investigation is needed to evaluate both the accident risk and the relevance of licensing recommendations such as restrictions on operating emergency, heavy-goods, and public transport vehicles for drivers with IDDM.													
Reviewers' Comments	This was a study in which the incidence of crash among individuals with diabetes (cases) was compared to the incidence of crash in a non-diabetic control population. Outcome data presented as odds ratios. We recalculated data as risk ratios for assessment.													

Table G-18. Demographic Characteristics of IDDM Cases and Non-Diabetic Sibling Controls

Characteristics	Cases		Controls	
	n	%	n	%
Age				
21–29	35	22.2	41	25.9
30–39	106	67.1	92	58.2
40–49	17	10.7	25	15.9
Sex				
Male	88	55.7	88	55.7
Female	70	44.3	70	44.3
Race				
White	154	97.5	154	97.5
Black	4	2.5	4	2.5
Age of IDDM onset (years)				
0–5	62	39.2		
6–9	46	29.1		
10–16	50	31.7		

Table G-19. Driving Patterns of IDDM Cases and Non-Diabetic Sibling Controls at Risk for Accidents

Characteristics	Cases	Controls
	IDDM cases (SD)	Non-diabetic siblings
Mean miles driven in past year (SD)	11,824 (12,467)	13,978 (13,342)
By sex		
Male	15,581 (14,911)	18,134
Female	7,607 (6,977)	9,311 (10,513)
By age		
21–29	16,503 (19,631)	14,650 (9,712)
30–39	10,708 (9,297)	14,417 (15,607)
40–49	9,427 (6,681)	10,700 (8,214)
Years driven	16.4 (5.3)	16.9 (5.7)
Age at which licensed	16.7 (1.5)	16.5 (1.3)

Table G-20. Number of accidents of IDDM cases and nondiabetic sibling overall by age, sex, mileage, and marital status

	Number of Drivers		Number of Accidents per 100 Drivers		
	IDDM Cases	Nondiabetic Siblings	IDDM Cases	Nondiabetic Siblings	*P* (Cases vs. Controls)
Total	127	127	14.17	7.09	17
Sex					
Male	68	68	14.71	10.29	.64
Female	59	59	13.56	3.39	.09
Age					
21-29	29	32	27.59	15.63	.55
30-39	83	74	12.05	5.41	.64
40-49	15	21	0.00	0.00	.98
Mileage per year					
1-9999	55	46	7.27	4.35	.80
10K-19,999	47	45	14.89	8.89	.74
≥20K	24	31	29.17	6.45	.36
Marital Status					
Married	92	92	9.78	3.26	.61
Not Married	35	35	25.71	17.14	.66

Table G-21. Number of accidents per 1,000,000 miles driven per year in IDDM cases and nondiabetic sibling overall by age, sex, mileage, and marital status

	Number of Drivers		Number of Accidents per 100 Drivers		
	IDDM Cases	Nondiabetic Siblings	IDDM Cases	Nondiabetic Siblings	*P* (Cases vs. Controls)
Total	121	121	10.40	3.91	.12
Sex					
Male	64	64	17.58	8.08	.94
Female	57	57	32.38	6.61	.03
Age					
21-29	29	30	57.64	30.33	.46
30-39	82	72	13.89*	5.35	.64
40-49	15	20	0.00	0.00	.98
Mileage per year					
1-9999	55	46	39.51	25.11	.81
10K-19,999	47	45	25.13	15.50	.70
≥20K	24	31	40.43	6.83	.33
Marital Status					
Married	91	88	9.52	2.84	.62
Not Married	35	34	55.99	29.92	.52

**P* <0.05 difference between age strata

Table G-22. Estimate parameters, standard errors of parameters, odds ratios, 95% confidence intervals around odds ratios, and P value for logistic

model depicting motor vehicle accident probability (yes/no) among 254 cases and controls

	b	SE	Odds Ratio	95% CI	*p*
Diabetic status (diabetic:control)	-0.012	0.645	0.99	(0.28, 3.50)	.98
Sex (f: m)	-0.891	0.866	0.41	(0.07, 2.33)	.31
Age (young: old)	0.113	0.052	3.10	(1.12, 8.58)	.03
Mileage/year (high: low)	0.000011	0.000019	1.12	(0.77, 1.62)	.55
Marital status (not married: married)	1.273	0.517			.01
Diabetic status/sex interaction	1.757	1.083	3.57	(1.30, 9.84)	.10
Female cases: Female controls	1.745	0.872	5.73	(1.04, 31.6)	.045
Female cases: Male cases	0.866	0.658	2.38	(0.65, 8.64)	.19
Female cases: Male controls	0.854	0.675	2.35	(0.63, 8.82)	.21

Reference: Stevens AB, Roberts M, McKane R, Atkinson AB, Bell PM, Hayes JR. Motor Vehicle Driving among Diabetics taking Insulin and Non-Diabetics. BMJ 2 September 1989 299:591-95														
Key Questions Addressed	1		2		3		4							
	✓													
Research Question	To determine whether rates of road traffic accidents were higher in diabetics treated with insulin than in non-diabetic subjects.													
Study Design	Case-control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	IDDM and non-insulin dependent diabetic patients aged 18-65 inclusive on 1 October 1986 who had used insulin for one year.												
	Exclusion Criteria	NR												
	Study population Characteristics	Poorly reported. Only characteristics reported are presented in Table G-23.												
	Generalizability to CMV drivers	Unclear												
Methods	Questionnaire completed under supervision of one of the authors included information on home monitoring of BG, experience of hypoglycemia, alcohol consumption, number of accidents since beginning insulin treatment, experience of hypoglycemia while driving, declaration of condition to the Driving and Vehicle Licensing Center and insurance company, and assessed on knowledge of the relevant legislation and the recommendations of the British Diabetic Association for drivers. A similar questionnaire was completed by cohort patients recruited from the dermatology and gastroenterology clinics.													
Statistical Methods	Contingency tables and chi-square tests were performed.(Table G-24)													
Quality assessment	Quality score=7.9	1	2	3	4	5	6	7	8	9	10	11	12	13
		N	Y	Y	Y	Y	Y	N	NR	Y	Y	Y	Y	Y
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency of motor vehicle accidents													
Results	Number of drivers reporting accidents from each group was not significantly different. See Table G-24.													
Authors' Comments	Diabetic drivers treated with insulin and attending clinics have no more accidents than non-diabetic drivers.													

Table G-23. Details on driving and alcohol consumption for diabetics taking insulin and non-diabetics. Figures are numbers (percentages) of subjects

	Diabetics (n=354)	Non-diabetics (n=302)
*Years driving licence held**		
<5	45 (13)	76 (25)
6-	49 (14)	70 (23)
11-	66 (19)	36 (12)
≥15	194 (53)	120 (40)
Frequency of alcohol consumption/week†		
None	129 (36)	82 (27)
<Once	146 (41)	136 (45)
2-3 Times	60 (17)	71 (24)
>3 Times	13 (4)	12 (4)
Unknown	6 (2)	1 (<1)
Annual distance travelled (km)‡		
<8000	113 (32)	99 (33)
8000-	106 (30)	91 (30)
17 700-	70 (20)	70 (23)
26 000-	29 (8)	20 (7)
≥32 000	32 (9)	20 (7)
Unknown	4 (1)	2 (1)
Driving area§		
Urban	232 (66)	199 (66)
Rural	116 (33)	99 (33)
Unknown	6 (2)	4 (1)

*$\chi^2=34$, $p<0{\cdot}001$. ‡$\chi^2=2{\cdot}66$, $p=0{\cdot}62$.
†$\chi^2=8{\cdot}4$, $p=0{\cdot}04$. §$\chi^2=0{\cdot}00$, $p=0{\cdot}97$.

Table G-24. Information on accidents for diabetics and non-diabetic drivers who had had one or more accidents

	Diabetics (n=354)	Non-diabetics (n=302)	Difference (%)	95% Confidence interval of difference	χ^2	p Value
Basic data	82 (23·2%)	75 (24·8%)	−1·7*	−8·3 to 4·9	0·25	0·62
Stratified for:						
Age and sex			−1·6	−8·2 to 5·0	0·23	0·63
Duration driving licence held			−1·5	−8·3 to 5·3	0·19	0·66
Alcohol consumption			−1·6	−8·2 to 5·0	0·23	0·63

*A rounding error exists.

Study Summary Tables (Key Question 2)

Reference: Cox DJ, Gonder-Frederick LA, Clarke WL. Driving Decrements in Type 1 Diabetes During Moderate Hypoglycemia. Diabetes February 1993;42:239-43.														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To determine driving decrements during and after hypoglycemia, and the patient's awareness of driving decrements.													
Study Design	Case control study													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	T1DM; insulin treatment since time of diagnosis												
	Exclusion Criteria	Chronic medication use (except insulin); significant diabetic complication as revealed by self-report and physical examination; history of hypoglycemia awareness; history of substance abuse												
	Study population Characteristics	Males: 12 Females: 13 Mean age: 14.6 years old (± 10.5) Mean HbA1: 10.8 (± 2.9%) Drivers license years Mean: 19 (± 13.2 yr) Average miles driven in past year: 6720 (± 5232)												
	Generalizability to CMV drivers	Unclear												
Methods	Participation in a research study examining the cognitive-motor effects of hypoglycemia was solicited by newspaper. In return for participation in a 2 day hospital based study, subjects were paid $100.00. 24 hours before reporting to the Research Center, participants discontinued long-acting insulin use. Patients were admitted to the General Clinical Research Center the evening before the study and were allowed to drive the driving simulator for 30 minutes to diminish practice effects. Fasting began after 2100. From 2300 to 0800 participants received IV regular human insulin to maintain euglycemia. At 0800 participants were connected to a closed-loop insulin/glucose infusion system. Insulin was infused at a variable rate to achieve target blood glucose levels. BG levels were examined every 10 minutes, with the participants blinded to their BG levels, BG target levels, whether it was an experimental or a control day, and the sequence of the BG fluctuations. Each participant drove the simulator for 4 minutes, 4 tests a day, for 2 consecutive days. Immediately pre and post-driving test, participants were asked "Would you choose to drive right now? Yes/No" On control day, participants were kept at euglycemia. On experiment day, participants were cycled through euglycemia, to mild hypoglycemia, to moderate hypoglycemia, and back to euglycemia, with 1hr between each test on both control and experimental days. Driving parameters were divided into two parameters: steering (swerving; spinning; time spent across midline; and time spent off the road) and speed control (smoothness of braking; smoothness of acceleration; speeding; very slow driving).													
Statistical Methods	Effects of hypoglycemia on driving were addressed using 2 x 2 repeat measures ANOVAs To determine whether driving decrements recovered, Students t test compared test-4 conditions. To determine whether the participants would choose to drive, yes/no responses were analyzed with the nonparametric Cochran Q test.													
Quality assessment	Quality Score=10	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	Hypoglycemia as a risk factor for motor vehicle driving performance decrements in individuals with DM													

Results	No significant driving performance decrement occurred during euglycemia following moderate hypoglycemia. During mild hypoglycemia only two (8%) of the participants demonstrated a global driving decrement. During moderate hypoglycemia 35% of the participants demonstrated a global driving decrement. During the moderate hypoglycemia portion of the experimental day, participants: • Swerved more (F = 4.3, P <0.05) • Spun more (F = 3.9, P <0.059) • Spent more time over the midline (F = 4.0, P <0.056) • Spent more time off the road (F = 6.4, P <0.02) • Drove < 30% of the posted speed limit (F = 4.9, P <0.04) No differences were apparent in participants decision to drive at baseline or recovery from moderate hypoglycemia. During both mild and moderate hypoglycemia, participants reported more often they would not drive. Driving experience during moderate hypoglycemia led to greater awareness of driving decrements, with 58% pre-test and 77% post-test of the participants unwilling to drive. In terms of the number of significant decrements, no difference occurred between patients who said they would or would not drive. Of the participants demonstrating global decrements, only 50% anticipated such decrements, and after driving, 25% were still willing to drive. Students t tests found no difference between those participants who did and did not demonstrate global decrements in terms of age, sex, IQ, duration of disease, absolute BG at time of testing, HbA_1, average miles driven in the past year, years driving experience, and self-reported history of automobile crashes.
Authors' Comments	Data suggest that neither mild hypoglycemia (3.6mM) nor recovery from brief moderate hypoglycemia were associated with disruption in driving performance during brief testing. Moderate hypoglycemia (2.6mM) was associated with driving performance decrements. Driving decrements were not associated with standard demographics, disease characteristics, or past driving behaviors, making it currently impossible to predict which individuals will experience driving decrements at moderate hypoglycemia.

<table>
<tr><td colspan="8">Reference: Cox DJ, Kovatchev BP, Gonder-Frederick LA, Clarke WL. Progressive Hypoglycemia's Impact on Driving Simulation Performance. Diabetes Care February 2000;23(2):163-70.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td>5</td></tr>
<tr><td></td><td colspan="2">✓</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>Research Question</td><td colspan="8">To evaluate whether progressive hypoglycemia leads to cognitive-motor and driving impairment.</td></tr>
<tr><td>Study Design</td><td colspan="8">Case control study</td></tr>
<tr><td>USPSTF Level</td><td colspan="8">II-2</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="7">T1DM a minimum of 2 years; insulin treatment since time of diagnosis; current driver</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="7">Use of medication that might influence hypoglycemia or driving performance.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="7">See Table G-25..</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="7">Unclear</td></tr>
<tr><td>Methods</td><td colspan="8">37 subjects were recruited through newsletters, notices posted in diabetes clinics, and direct physician referral.
Subjects were admitted to the General Clinical Research Center the evening before the study, where they received a physical exam and practiced driving the simulator for 15 minutes (or as long as it took to become comfortable with its operation). While driving the simulator, subjects practiced rating their symptoms and driving performance on a 0-6 scale, were shown a bottle of orange soda in the glove compartment, and were instructed to drink the soda or pull off the road and discontinue driving if they thought their BG was too low.
BG was maintained at 5.6-8.3mmol/l with IV human insulin overnight, after subjects were given dinner and a bedtime snack. Subjects then fasted on the morning of the study, and no caffeinated beverages were consumed after admission.
The morning of the study BG began at the 5.6-8.3 level and remained there for the first hour of testing. BG was then progressively lowered to 2.2mmol/l. Arterialized blood was sampled for BG every 5 minutes, with subjects rating neurogenic and neuroglycopenic symptoms and estimating their BG. Subjects were blinded to BG manipulations and actual BG levels.
Subjects were fitted with an EEG cap to monitor brain activity during the test.
During the first hour the subjects watched a videotape of someone else driving the simulator for 30 minutes, then drove the simulator themselves for 30 minutes.
Subjects were instructed that the study was investigating the effects of high and low BG on brain wave activity and driving behaviors.</td></tr>
<tr><td>Statistical Methods</td><td colspan="8">z scores calculated for continuous variables, comparison of BG ranges.
Chi-square tests
Multiple regression
Discriminant analysis</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score=9.2</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="8">Hypoglycemia as a risk factor for motor vehicle driving performance decrements in individuals with DM</td></tr>
<tr><td>Results</td><td colspan="8"><u>Hypoglycemia and Driving Impairment</u>
During hypoglycemia, subjects engaged in the following behaviors:
• Driving across the midline
• Speeding
• Used brakes more on open road
At one of the three hypoglycemia BG ranges, driving performance was 3.3 SDs worse than the subjects average euglycemic performance.
During the last 15 minutes of hypoglycemia (compared to the last 15 minutes of euglycemia) subjects failed to stop at stop signs significantly more often and were involved in more crashes at sudden stops.
Awareness and corrective behaviors:
Global self-evaluations were significantly elevated during the mild and moderate hypoglycemia events.
Subjects demonstrating significant impairments were more likely to take some form of corrective action.
During hypoglycemic BG, driving was significantly impaired, and subjects were aware of their impaired driving. Corrective action usually did not take place until BG was <2.8mmol/l. Driving impairment was related to increased neurogenic symptoms and theta-wave activity. Awareness of driving impairment was related to neuroglycopenic symptoms, increased beta-wave activity and awareness of hypoglycemia. High beta, low theta activity and awareness of both hypoglycemia and the need to treat low BG influenced corrective behavior. (Table G-26)</td></tr>
</table>

Authors' Comments	Driving performance is significantly disrupted at relatively mild hypoglycemia. Subjects demonstrated a hesitation to take corrective action. The longer treatment is delayed, the greater the neuroglycopenia, which precludes corrective behaviors. Patients should treat themselves while driving as soon as low BG and/or impaired driving is suspected and not when their BG is in the 5.0-4.0 mmol/l range without prophylactic treatment. (Table G-27)

Table G-25. Subject Characteristics for those with and without a recent history of severe hypoglycemia

	No history of severe hypoglycemia	≥2 episodes of severe hypoglycemia in past 12 months	*P*=	All subjects
N=	14	23		
Age: years	33.4 (4.7)	36.5 (8.1)	0.21	35.3 (7.1)
Duration of diabetes: years	16.0 (11.8)	18.5 (8.8)	0.47	17.5 (10.0)
Impaired/normal hypoglycemic awareness	4/10	14/9	0.12	18/19
Sex (m/f)	7/7	9/14	0.75	16/21
Units of insulin: U/day kg^{-1}	0.64 (0.17)	0.59 (0.17)	0.34	0.61 (0.17)
HbA_{1c} (%)	8.6 (1.3)	8.4 (2.0)	0.74	8.5 (1.8)
BMI	25.5 (4.1)	23.0 (3.1)	0.04	23.9 (3.7)
Auto crashes per 1,000,000 miles	20.1 (56.0)	43.2 (161.0)	0.62	34.7 (131.0)
Motor violations per1,000,000 miles	20.1 (46.0)	43.0 (109.0)	0.38	34.3 (90.1)
Average miles driven/year	13,594 (11,147)	6,839 (3,951)	0.04	9,395 (8,089)

Data are n or means (SD)

Table G-26. Performance at three levels of hypoglycemia based on z scores derived from individual euglycemic performance

Variable	Blood glucose level		
	4.0–3.3 mmol/L	3.3–2.8 mmol/L	<2.8 mmol/L
Driving performance z-score deviation from euglycemia			
SD steering	0.04 (NS)	-0.02 (NS)	-0.04 (NS)
Off road	0.25 (NS)	0.45 (NS)	0.57 (NS)
Risk midline	0.05 (NS)	0.17 (NS)	0.11 (<0.01)
Low speed	0.01 (NS)	-0.05 (NS)	0.37 (NS)
High speed	0.23 (<0.01)	0.56 (<0.001)	0.26 (NS)
SD Speed	-0.09 (NS)	0.09 (NS)	0.23 (NS)
Inappropriate braking	0.00 (NS)	0.61 (<0.05)	0.00 (NS)
Composite driving impairment score	0.83 (<0.01)	1.83 (<0.005)	1.52 (<0.005)
% subjects significantly impaired	12	26	16
Awareness deviation from euglycemia			
Difficulty driving rating	0.30 (<0.05)	0.35 (NS)	0.54 (<0.05)
% of subjects who detected their driving impairment	21	22	25
% subjects who detected hypoglycemia	15	33	79
Corrective behaviors			
Self-treated	2 (NS)	1 (NS)	8 (<0.05)
Stop driving	1 (NS)	1 (NS)	5 (NS)
% subjects who took corrective action	5	3	22

P-values in parentheses

Table G-27. Post-hoc comparisons of different subgroups on the Composite Driving Impairment scores

Comparison groups	Mean composite driving impairment scores	*P*=
Impaired vs. normal hypoglycemia awareness	1.0 vs. 1.0	0.21
Recent history vs no history of severe hypoglycemia	1.3 vs. 1.7	0.61
Men vs women	1.4 vs 1.6	0.82
Low BG in previous 48 hours vs. no low BG	1.9 vs 1.2	0.45
≤2 vs. ≥3 insulin injections per day	1.2 vs. 1.8	0.50

Reference: Driesen NR, Cox DJ, Gonder-Frederick L, Clarke W. Neuropsychology 1995 (9) 2:246-53														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To evaluate the effects of hypoglycemia on cognitive processing speed as measured by reaction time (RT) in IDDM.													
Study Design	Crossover study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	IDDM; insulin dependent since diagnosis.												
	Exclusion Criteria	Major psychiatric problems; severe diabetic complications; history of substance abuse.												
	Study population Characteristics	Males: 12 Females: 13 Mean age: 35.5 (± 14) Duration of diabetes (years): 14.3 (± 10.6) Age at onset: 21 (± 12) Glycosylated hemoglobin: 10.6 (± 0.58) (Table G-28)												
	Generalizability to CMV drivers	Unclear												
Methods	Participation in a research study examining the cognitive effects of hypoglycemia was solicited by newspaper and in clinics. In return for participation, subjects were paid $100.00. 36 hours before reporting to the Research Center, participants discontinued long-acting insulin use. Patients were admitted to the General Clinical Research Center the evening before the study and were allowed to practice the RT tests for 10 minutes to diminish practice effects. Fasting began after 2100. From 2300 to 0800 participants received IV regular human insulin to maintain euglycemia. At 0800 participants were connected to a closed-loop insulin/glucose infusion system. Insulin was infused at a variable rate to achieve target blood glucose levels. BG levels were examined every 10 minutes, with the participants blinded to their BG levels, BG target levels, whether it was an experimental or a control day, and the sequence of the BG fluctuations. Each participant performed the RT tests, 4 tests a day, for 2 consecutive days. At all sessions, RT tests were given in the following sequence: simple, choice-side, choice-direction, and then complex reaction time. On control day, participants were kept at euglycemia. On experiment day, participants were cycled through euglycemia, to mild hypoglycemia, to moderate hypoglycemia, and back to euglycemia, with 1hr between each test on both control and experimental days. 15 of the 16 subjects agreed to return for identical protocol repeat testing in three months.													
Statistical Methods	Effects of hypoglycemia on speed response and accuracy were addressed using 2 x 2 repeat measures MANOVAs Effect sizes were used to compare the sensitivity of the RT tasks to hypoglycemia. Cohen's d was used to measure effect size for paired observations. The relationship between participant characteristics and hypoglycemia sensitivity was established by correlating these scores with individual difference variables such as age. Residual score approach was used to examine similarities in hypoglycemic sensitivity on the initial and repeat hospitalization.													
Quality assessment	Quality Score=8.18	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y		
	Low	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	

Results	**During the moderate hypoglycemia portion of the experimental day, participants:** Were significantly slower on all reaction time tasks. Differed significantly, on an individual basis, in their sensitivity to hypoglycemia. More complex tasks were not associated with larger differences between baseline, mild, or moderate hypoglycemia. There was no significant relationship between residual scores at mild and moderate hypoglycemia several individual difference variables such as Full Scale IQ, Performance IQ, Verbal IQ, age of diabetes onset, glycosylated hemoglobin, BG attained at hypoglycemia and number of times unable to treat hypoglycemia in last 12 months. There was no significant difference between males and females in hypoglycemia sensitivity as measured by residual scores. **Repeat Testing Period (3 months after initial testing)** Effect of session was significant for all the RT tasks: RT during moderate hypoglycemia was significantly slower than during baseline euglycemia. RT during mild hypoglycemia was not significantly different than during baseline euglycemia. Deficits in RT performance on an individual basis were inconsistent across initial and repeat hospitalizations. Averaged across RT tasks, correlations between residual scores during mild and moderate hypoglycemia on the repeat day were not correlated significantly with the same measures on the initial experiment day. Moderate hypoglycemia significantly increases RT. In some individuals, mild hypoglycemia may also slow cognitive processing. No relationship was found between task complexity and RT. Individuals are less likely to produce errors on simple tasks. Individual response to hypoglycemia varies greatly and was not consistent across time. (Table G-29;Table G-30;Table G-31;Table G-32)
Authors' Comments	A better understanding of the transitory and enduring factors that affect hypoglycemia sensitivity is needed.

Table G-28. Participant Characteristics

Variable	Mean ± *SD*	Range
Age (years)	35.5 ± 14	19–67
Wechsler Adult Intelligence Scale—Revised score	109 ± 11	90–137
Duration of diabetes (years)	14.3 ± 10.6	2–36
Age at onset	21 ± 12	5–44
Glycosylated hemoglobin	10.6 ± 0.58	6–16.7
Participant data		
	%	*n*
Insulin regimen dose		
1 fixed	16	4
2 fixed	8	2
3 or more fixed	32	8
Variable (multiple injection)	44	11
Occupation		
Unskilled labor	16	4
Trades	4	1
Clerical	16	4
Professional	28	7
College student	36	9
Education		
High school	9	3
Some college	40	10
Bachelor's degree	32	8
Postgraduate	16	4

Table G-29. Repeated Measures Multivariate Analysis of Variance on Absolute Reaction Time

Task	Effect	F^a	*df*	$p <$
Simple	Day	6.66	1, 18	.05
	Session	6.65	3, 16	.01
	Day × Session	4.68	3, 16	.05
Choice-side	Day	8.15	1, 18	.05
	Session	16.64	3, 16	.001
	Day × Session	7.31	3, 16	.01
Choice-direction	Day	5.68	1, 18	.05
	Session	5.26	3, 16	.01
	Day × Session	8.53	3, 16	.001
Complex-side	Day	4.43	1, 18	.05
	Session	8.62	3, 16	.001
	Day × Session	4.40	3, 16	.05
Complex-direction	Day	12.60	1, 18	.05
	Session	2.09	3, 16	*ns*
	Day × Session	3.59	3, 16	.05

[a]According to Wilks's lambda criterion.

Table G-30. Comparison of BG Values (mg/dl) Attained on Initial and Repeat Hospitalization

Task	Mild	Moderate
Simple	−.39	−.68
Side	−.19	−.59
Direction	−.06	−.55
Complex-side	−.01	−.58
Complex-direction	−.17	−.44

Table G-31. Comparison of Average RT at Mild and Moderate Hypoglycemia to Average RT of Slowest Euglycemia Testing Session

	Hypoglycemia					
	Slower than euglycemia		Faster than euglycemia		Equal to euglycemia	
Task	*n*	%	*n*	%	*n*	%
Simple						
mild	8	38	13	62	0	
moderate	10	48	10	48	1	4
Choice-side						
mild	7	28	14	56	0	
moderate	14	64	8	37	0	
Choice-direction						
mild	8	38	13	62	0	
moderate	14	64	8	37	0	
Complex-side						
mild	4	19	16	76	1	5
moderate	13	59	9	41	0	
Complex-direction						
mild	4	19	17	81	0	
moderate	12	55	10	46	0	

Table G-32. Task Complexity and Effect Size

Task	Mild	Moderate
Simple	−.39	−.68
Side	−.19	−.59
Direction	−.06	−.55
Complex-side	−.01	−.58
Complex-direction	−.17	−.44

<table>
<tr><td colspan="15">Reference: Lobman R, Smid Henderikus GOM, Pottag G, Wagner K, Heinze H-J, Lehnert H. The Journal of Endocrinology and Metabolism 2000 (85) 8:2758-2766</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="2">1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td></tr>
<tr><td colspan="2"></td><td colspan="2">✓</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="14">To delineate cognitive adaptation after induction of hypoglycemia into single components, i.e., stimulus selection, response choice, and reaction speed.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case control study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-3</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Type 1 Diabetes Mellitus.
Healthy (non-diabetic)</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Signs or symptoms of autonomic or peripheral neuropathy by diabetic or other causes; retinopathy, peripheral vascular disease, hypertension, chronic heart failure, and renal or hepatic diseases.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">Males: 12
Females: 13
(Table G-33)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Each subject was studied in the morning following a 12 hr. fast. Caffeine and nicotine were not allowed.
All subjects received a euglycemia clamp. BG was monitored by continuous and intermittent sampling.
Dextrose, saline, and regular insulin were infused.
A three phase model of clamping was as follows: a hyperinsulinemic euglycemic phase, followed by a stepped phase plasma glucose reduction scheduled at every 20 minutes over 1.5 hours to a final plateau of 2.6mmol/L. The hypoglycemia plateau phase lasted for 30 minutes, after which glucose infusion was increased to restore euglycemia. Each plateau phase was clamped for 30 minutes in order to study the electrophysiological parameters.
At fixed BG levels blood samples were taken for measurements of counterregulatory hormones and BG levels. BG was taken after the hypoglycemia clamp phase and after reach the second euglycemia level.
Simultaneously with blood sampling, subjects participated in a semiquantitative symptom score questionnaire, including autonomic, neuroglycopenic, and not clearly attributable (weakness, hunger, speech disorder, double images, nausea, paresthesia)
During each of the three plateaus, subjects were administered a selective attention task (a sequence of colored letters was presented, and the letters in one color had to be selected to decide whether they required right hand movement, left hand movement, or no movement).</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Effects over time on symptom awareness were assessed by a general linear model with repeated measures.
Effects over time on neuroendocrine response was assessed by a general linear model with repeated measures.
ERP was averaged separately for each stimulus type, clamp condition, subject, and response side and used for MANOVA analyses.
A second set of MANOVA analyses was performed to find the onset latencies of the SN and LRP in each clamp condition and group.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score=10.0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">The effect of Hypoglycemia on a variety of cognitive functions.</td></tr>
</table>

Results	**Counterregulatory hormone response** (Table G-34) **Healthy participants with BG of 2.8mmol/L:** Adrenaline, glucagon, ACTH, and cortisol increased significantly. Noradrenaline response did not reach statistical significance. **Diabetic participants with BG of 2.8mmol/L:** Adrenaline, noradrenaline, and cortisol increased. Augmentation of glucagon and ACTH secretion did not reach statistical significance. **Symptom Awareness** Autonomic and neuroglycopenic symptom scores increased significantly during stepped hypoglycemia for both the healthy and diabetic participants. There was no statistically significant difference between groups at the different time points. **Neurophysiological Data** RTs increased as a result of the hypoglycemia clamp. RTs increased by 27msec in the healthy group during hypoglycemia, compared to initial euglycemia baseline. In the T1DM group, RTs also increased during hypoglycemia but no more than in the healthy controls. Overall difference in RTs between the groups was not significant. Across groups, restoring euglycemia resulted in significantly shorter RTs. RTS did not significantly decrease in the healthy group. RTs did decrease significantly in the T1DM group. Group by test-phase interaction did not reach significance. No baseline vs. post-treatment euglycemia comparisons reached significance. There were no significant effects on error frequencies of hypoglycemic treatment, nor of the restoration of euglycemia. Results indicate that induction of hypoglycemia produced comparable effects on task performance in the healthy and T1DM subjects. Hypoglycemia treatment produced a large frontally maximal negative shift in the ERPs that started and ended later in the healthy volunteers than in the T1DM volunteers. Positivity visible in the restored euglycemia waveforms was most prominently present in the healthy group and of only minor significance in the T1DM group. Results of the tests of difference potentials of SN and LRP indicate that hypoglycemia delayed the selection of a stimulus on the basis of its color (SN) and also delayed selection of the motor responses (LRP) on the basis of the letter shape in the healthy and T1DM subjects. This is in agreement with the behavioral results showing that the RTs of the T1DM group returned to baseline after restoration of euglycemia but not those of the control group. (Table G-35.)
Authors' Comments	Cognitive adaptation processes to hypoglycemia can be dissected into more elementary components such as stimulus selection, response choice, and reaction speed in both T1DM patients and healthy subjects. A direct effect of these cognitive impairments on hypoglycemia is still speculative but of great clinical relevance.

Table G-33. Clinical characteristics of subjects studied

	Nondiabetic subjects	Diabetic subjects
n	12	12
Gender (female/male)	8/4	5/7
Age (yr)	27 ± 3 (range, 24–32)	31 ± 7 (range, 20–43)
Duration of diabetes (yr)	0	7.8 ± 8.6 (range, 1–29)
HbA_{1c} (%)		7.38 ± 1.8
Body mass index (kg/cm2)	22.6 ± 1.8	24.2 ± 3.9

Table G-34. Data of hormone analysis (mean concentration of adrenaline, noradrenaline, cortisol, ACTH) at the different time points for both investigated groups

	Time (min)	Baseline (mean ± sd)	Maximum (mean ± sd)	Relative increase (%) (mean ± sd)
Adrenaline (ng/L)	IDDM	56.8 ± 39.9	282.6 ± 374.0	611 ± 395[a]
	Control group	33.8 ± 19.0	586.4 ± 322.7	2721 ± 1859[a]
Noradrenaline (ng/L)	IDDM	407.6 ± 123.8	497.6 ± 178.7	152 ± 30
	Control group	412.5 ± 97.1	507.8 ± 88.8	154 ± 33
Cortisol (nmol/L)	IDDM	353.7 ± 119.6	585.2 ± 238.1	231 ± 56
	Control group	340.1 ± 143.5	783.9 ± 263.1	261 ± 71
ACTH (pmol/L)	IDDM	4.4 ± 1.0	14.5 ± 21.0	423 ± 519[b]
	Control group	3.3 ± 1.3	31.2 ± 33.2	1159 ± 889
Glucagon (pmol/L)	IDDM	170.9 ± 80.2	193.1 ± 67.7	136 ± 23[b]
	Control group	225.4 ± 87.3	303.0 ± 103.5	184 ± 57

[a] $P < 0.01$.
[b] $P < 0.05$.

Table G-35. Averaged mean RT, total error frequencies (Terr), false alarms (FA) onset latencies of the SN, and LRP

	RT (ms)	Terr (%)	FA (%)	SN[a] (ms)	LRP[a] (ms)
Healthy controls					
Eu1	441	5.0	0.7	220	284
Hyp	468	8.9	1.7	252	356
Eu2	449	8.8	0.9	212	340
Type-1					
Eu1	470	7.3	2.1	164	396
Hyp	500	12.8	5.0	236[b]	452
Eu2	463	10.3	3.7	196	396

These data were obtained in pretreatment (Eu1), posttreatment (Eu2) and hypoglycemia (Hyp) conditions, for each of the groups.
[a] At least 40-ms interval with $P < 0.01$.
[b] 10 Epochs (80 ms) with $P < 0.05$.

<table>
<tr><td colspan="15">Reference: Weinger K, Kinsley BT, Levy CJ, Bajaj M, Simonson DC, Cox DJ, Ryan CM, Jacobson AM. The American Journal of Medicine 1999 (107) 246-53</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="5"></td></tr>
<tr><td></td><td colspan="2">✓</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="5"></td></tr>
<tr><td>Research Question</td><td colspan="14">To delineate the factors that influence judgements of safe driving ability during hypoglycemia.</td></tr>
<tr><td>Study Design</td><td colspan="14">Crossover study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-3</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Type 1 Diabetes Mellitus, duration 3-15 years
Aged 19 to 50 years old</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">No history of severe hypoglycemia during previous 2 years.
No evidence of diabetes complications (autonomic or peripheral neuropathy proliferative retinopathy, or diabetic nephropathy).</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">Males: 30
Females: 30
Mean age: 33 (± 9) years
Duration of disease: 9 (± 3) years
HbA_{1c}: 8.7% (± 1.0%)
(Table G-36)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Subject participation solicited mailings to the clinic population of the Joslin Diabetes Center and through advertisements in Boston area newspapers.
Subjects arrived at the clinic in the morning having not used the morning insulin dose.
All subjects underwent a stepped hypoglycemia clamp. Serum glucose levels were reduced from 120 mg/dL to 80, 70, 60, 50, and 40 mg/dL during 190 minutes. BG levels were maintained for 25 minutes at each plateau. Serum glucose was measured every 5 minutes.
During the last 15 minutes of each glucose plateau patients completed a mood &symptom questionnaire and neurophysiological test, estimated their glucose level, and reported whether they could drive safely. The neurophysiological test included measures of selective and sustained attention and psychomotor speed (Multi-Choice Reaction Time), mental flexibility, and visual-spatial skills.
Subjects were blinded to actual BG levels.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">A summary measure of overall cognitive functioning at each glycemic plateau was calculated by converting individual test scores to Z scores based on the baseline mean and standard deviation.
Continuous data were reported as mean ± SD.
Paired t tests, Pearson correlation coefficients, and repeated measures analysis of variance. McNemer's test for dependent samples and Fisher's exact test for bivariate independent samples were used.
Multilevel modeling.
Repeated measures logistic regression.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score=10.0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">The effect of Hypoglycemia on a variety of cognitive functions.</td></tr>
</table>

Results	Of the 48 subjects who returned questionnaires about driving history, 20 (42%) reported having one or more driving accidents since being diagnosed with diabetes and 5 (10%) reported personal injury associated with the accident. **Perception of driving safely:** • With increasing severity of hypoglycemia there was an overall trend for a decreasing proportion of subjects who judged that they could drive safely (P <0.04) (Table G- 37) • 30% of subjects perceived that they could not drive safely during a euglycemic episode of 120mg/dL • 13% of subjects perceived that they could not drive safely during both euglycemic episodes (120 and 80mg/dL) • 8% of subjects did not perceive safe driving at any glucose level • 38% of subjects rated themselves as able to drive safely at serum glucose level 50mg/dL • 22% of subjects rated themselves as able to drive safely at serum glucose level 40mg/dL **Effects of Sex and Age:** • Men were more likely than women to judge that they could drive safely (P <0.005), especially during mild hypoglycemia (60mg/dL) • Age was associated with driving ability, with more middle-aged subjects (35-50 years) than young subjects (<25 years) reporting that they could drive safely as glucose levels fell off. At a serum glucose of 40mg/dL, 0% of subjects <25 years. judged that they could drive safely, compared to 30% of subjects aged 35-50. • At 60mg/dL, 33% of younger subjects, compared with 61% of middle-aged subjects, judged that they could drive safely. • There was no sex by age interaction. • Duration of diabetes was not related to judgement about driving ability. **Cognitive Function and Driving:** • Performance on the Cognitive tests deteriorated during hypoglycemia, with subjects maintaining baseline levels of performance on only two tasks out of five. • No subjects were severely impaired at a serum glucose level of 60mg/dL, 1 subject was severely impaired at a serum glucose level of 50mg/dL, and 11 subjects were severely impaired at a serum glucose level of 40mg/dL. • The majority of cognitively impaired subjects judged that they could not safely drive at serum glucose level of 60, 50, and 40mg/dL. When the serum glucose level was 40mg/dL, 23% of subjects who were somewhat cognitively impaired or cognitively impaired judged that they were able to drive safely.(Table G-38) **Symptom Experience and Glucose Estimation:** • Neurogenic and neuroglycopenic symptoms were more intense as severity of hypoglycemia increased. They had similar effects on the perception of safe driving. • More patients with few or no symptoms judged that they were able to drive safely compared with those who were symptomatic (Table G-39). • The ability to recognize hypoglycemia improved as hypoglycemia became more severe. • Cognitive impairment did not affect the perceived ability to drive in patients who recognized that they were hypoglycemic. • None of the severely impaired subjects who recognized hypoglycemia reported that they could drive safely. • Actual glucose level, cognitive index score, error in BG estimation, intensity of symptoms, and subjects' age and sex were associated with perceiving safe driving ability, but self-rating of driving experience, the number of automobile accidents, and duration of diabetes were not.
Authors' Comments	Most patients with T1DM perceived that they could not drive safely during moderate hypoglycemia. However, many patients, particularly those who may not have symptoms of hypoglycemia or who are inaccurate in estimating BG level could benefit from educational reinforcement of safe driving habits, particularly to check BG before driving and to treat, or not to drive at, glucose levels below 70mg/dL.

Table G-36. Characteristics of the 60 Subjects with type 1 Diabetes, Stratified by Sex

Characteristic	Number (percent) or Mean ± SD	
	Men (n = 30)	Women (n = 30)
Age (years)	36 ± 9	30 ± 8*
18 to 25	4 (13)	11 (37)
26 to 35	11 (37)	11 (37)
36 to 50	15 (50)	8 (27)
Duration of diabetes (years)	9 ± 3	8 ± 3
Education (years completed)	16 ± 2	16 ± 2
Hemoglobin A_{1c} level (%)†	8.6 ± 1.0	8.7 ± 1.0
Years driving‡	21 ± 8	15 ± 18*
Miles driven per year‡	20,000 ± 2,000	12,000 ± 1,000

* $P < 0.05$ comparing men with women.
† Normal range, 4.0% to 6.0%.
‡ Available for 48 patients.

Table G- 37. Perceived Safe Driving Ability and Cognitive Test and Symptom Scores at Baseline and Each Serum Glucose Plateau*

	Target Glucose Plateau					
	120 mg/dL	80 mg/dL	70 mg/dL	60 mg/dL	50 mg/dL	40 mg/dL
Perceived ability to drive safely (n, %)	42 (70)	45 (75)	38 (63)	33 (55)	23 (38)	13 (22)
Trail Making Test						
Part A score	19 ± 5	18 ± 5†	17 ± 4‡	17 ± 4‡	17 ± 4‡	20 ± 9
Part B score	44 ± 15	42 ± 13	54 ± 19§	53 ± 19§	44 ± 18	62 ± 49‡
Choice Reaction Time (seconds)	0.52 ± 0.1	0.51 ± 0.1	0.54 ± 0.1†	0.56 ± 0.1§	0.56 ± 0.1§	0.65 ± 0.2§
Digit Vigilance Test						
Items scanned	814 ± 142	770 ± 128§	857 ± 196‡	772 ± 144§	734 ± 154§	628 ± 154§
Omission errors (%)	5.6 ± 4.3	5.1 ± 4.6	5.4 ± 4.3	5.9 ± 4.4	5.6 ± 5.3	8.3 ± 8.5†
Subtraction Test						
Score	9.5 ± 0.7	9.6 ± 0.8	9.8 ± (0.5)†	9.6 ± (0.8)	9.6 ± (0.9)	9.1 ± (1.6)
Time (seconds)	33 ± 14	33 ± 11	34 ± (13)	35 ± (14)	36 ± (15)†	44 ± (25)§
Symptoms						
Neurogenic	0.3 ± 0.5	0.4 ± 0.7	0.5 ± 1.0†	0.8 ± 1.1§	1.3 ± 1.5§	2.3 ± 1.5§
Neuroglycopenic	0.6 ± 0.6	0.8 ± 0.8†	1.0 ± 1.0§	1.3 ± 1.2§	1.5 ± 1.3§	2.2 ± 1.4§

* High test scores indicate poor performance except for subtraction test score and number of items scanned on the Digit Vigilance Test. Baseline glucose level was 120 mg/dL.
† $P < 0.05$ by repeated measures of analysis with contrasts, compared with baseline.
‡ $P < 0.01$ by repeated measures of analysis with contrasts, compared with baseline.
§ $P < 0.001$ by repeated measures of analysis with contrasts, compared with baseline.

Table G-38. Frequency of Cognitive Impairment during Hypoglycemia and Association with Perceived Safe Driving Ability*

Serum Glucose Plateau	Number (percent)		
	Not Cognitively Impaired	Somewhat Cognitively Impaired	Severely Cognitively Impaired
Target of 60 mg/dL†	50 (83)	10 (17)	0
Perceived safe driving‡	29 (58)	4 (40)	NA
Target of 50 mg/dL†	52 (87)	7 (12)	1 (2)
Perceived safe driving‡	19 (37)	4 (57)	0
Target 40 mg/dL†	34 (57)	15 (25)	11 (18)
Perceived safe driving‡	7 (21)	4 (27)	2 (18)

* Patients were classified as not cognitively impaired during hypoglycemia if their cognitive index Z score was <1 SD below their baseline mean value; as somewhat cognitively impaired if their score was 1 to 2 SD below their baseline mean value; and as severely cognitively impaired if their score was >2 SD below their baseline mean value.
† Number (percent) of patients in that category of cognitive impairment at the target glucose level.
‡ Number (percent) of those perceiving safe driving among those with that level of cognitive impairment.

Table G-39. Frequency of Neurogenic and Neuroglycopenic Symptoms during Hypoglycemia and Perceived Ability to Drive Safely

Serum Glucose Plateau	Symptoms, Number (percent)		
	None to Mild*	Moderate	Severe
Symptoms at target of 60 mg/dL			
Neurogenic†	46 (77)	10 (17)	4 (7)
Perceived safe driving‡	33 (72)	0	0
Neuroglycopenic†	38 (63)	15 (25)	7 (12)
Perceived safe driving‡	24 (63)	8 (53)	1 (14)
Symptoms at target of 50 mg/dL			
Neurogenic†	40 (67)	11 (18)	9 (15)
Perceived safe driving‡	19 (48)	4 (36)	0
Neuroglycopenic†	31 (52)	20 (33)	9 (15)
Perceived safe driving‡	14 (45)	8 (40)	1 (11)
Symptoms at target of 40 mg/dL			
Neurogenic†	18 (30)	23 (38)	19 (32)
Perceived safe driving‡	6 (33)	7 (30)	0
Neuroglycopenic†	20 (33)	23 (38)	17 (28)
Perceived safe driving‡	3 (15)	8 (35)	2 (12)

* None to mild = mean symptom score <1.5; moderate = mean symptom score between 1.5 and 3.0; intense = mean symptom score >3.0.
† Number (percent) of patients with that category of symptoms at the target glucose level.
‡ Number (percent) of those with perceived safe driving among those with that level of symptoms.

Table G-40. Subjects' (n=60) Ability to Estimate BG Level at Baseline (120mg/dL) and Each Glucose Plateau

	Target Serum Glucose Plateau, Percent or Mean ± SD					
	120 mg/dL	80 mg/dL	70 mg/dL	60 mg/dL	50 mg/dL	40 mg/dL
Error category*						
Accurate	23	37	28	47	68	88
Benign errors	63	42	22	0	0	0
Serious errors	13	22	50	53	32	12
Estimated glucose level (mg/dL)	131 ± 82	130 ± 82	140 ± 87	117 ± 81	96 ± 80	65 ± 44
Estimation error† (mg/dL)	13 ± 83	48 ± 82	69 ± 87	55 ± 81	44 ± 80	21 ± 44

* Accurate estimates are within 20% of the actual blood glucose level. Serious errors involve either dangerous failure to treat hypoglycemia or erroneous treatment (28).
† Estimation error = estimate minus actual glucose level.

Table G-41. Factors Independently Associated with Perceived Ability to Drive Safely during Six Glucose Levels

Variable (unit)	Odds Ratio (95% confidence interval)	*P* Value
Age (10-year increase)	2.2 (1.3–3.9)	0.005
Female sex	0.4 (0.1–0.9)	0.03
Serum glucose level (10 mg/dL increase)	1.2 (1.0–1.3)	0.03
Symptoms of hypoglycemia	0.3 (0.2–0.5)	0.0001
Cognitive index (per SD)	1.8 (1.0–3.1)	0.04
Glucose estimation error (10 mg/dL increase)	1.1 (1.0–1.1)	0.001

<table>
<tr><td colspan="15">Reference: Heller SR, Herbert M, Macdonald IA, Tattersall RB. The Lancet August 15 1987:359-63</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="5"></td></tr>
<tr><td></td><td colspan="2">✓</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="5"></td></tr>
<tr><td>Research Question</td><td colspan="14">To assess which symptoms and physiological changes are responsible for hypoglycemic awareness and to establish whether the loss of warning signs is associated with a reduced catecholamine response.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case control study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-3</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Diabetes Mellitus
Healthy</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">See Table G-42 below</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Diabetic subjects arrived at the clinic at 0700h having not used the morning insulin dose. Porcine insulin was administered to keep BG between 4 – 6mmol/L for at least 5 hours before the experiment began.
Non-diabetic subjects arrived at 1300h having begun fasting at 0800h
A modified euglycemia clamp was used to maintain BG at predetermined levels. Glucose was administered by pump and adjusted every 2-5 minutes according to BG levels.
BG was maintained for 30 minutes at four successive levels: 4-5mmol/L, 3-2mmol/L, 2.5mmol/L, and 4.5mmol/L. At each level, physiological measurements were made blood was taken for adrenaline estimation. BG was allowed to fall by switching off the glucose infusion temporarily and increased by speeding up the infusion rate. 20 minutes was taken to alter BG between 2 levels.
Subjects were blinded to actual BG levels and the order in which they were manipulated.
Seven physiological measurements were scored by subjects as absent, mild, moderate, or severe.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Results were expressed as mean and SEM. ANOVA and regression were used.
t-tests were used when F-tests indicated significant treatment-by-time interactions.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Results</td><td colspan="14">BG levels: Targets were achieved in both diabetic and non-diabetic subjects.
Awareness of Hypoglycemia: At 2.5 mmol/L 9/10 healthy subjects were aware of LBG, compared with 4/15 diabetic subjects.
Symptom score: Healthy subjects and the 4/10 diabetic subjects noted sweating, tremor, flushing of the face, blurring of vision, palpitations, or drowsiness.
Tremor: Reduction to 2.5mmol/L was accompanied by increased tremor in healthy subjects but not in the 11/15 unaware diabetics. Tremor readings were obtained in only 3 aware diabetic subjects.
Heart rate and Blood pressure: Basal heart rate was similar in all groups and did not change significantly during the experiment. At 2.5mmol/L, diastolic BP fell significantly in healthy subjects and the 4/15 symptom aware diabetics but not in the 11/15 symptom unaware diabetics.
Sweating: Basal rates were similar in all groups. At the 2.5mmol/L BG level there was a significant increase in sweat evaporation in the healthy and 4/15 diabetics, with the 11/15 diabetics showing no change.
Reaction Time: At initial BG of 4.5mmol/L, reaction time for healthy subjects was significantly shorter than in the diabetic groups. At BG 3.2mmol/L reaction time was longer in all three groups. Reaction time remained prolonged in all three groups at 2.5 mmol/L.
Adrenaline: Basal adrenaline was similar in all groups. At BG 3.2mmol/L adrenaline increased for healthy subjects and 4/15 aware diabetics. At BG 2.5mmol/L all groups demonstrated significant increases in adrenaline, with increased increments in the healthy and 4/15 aware diabetic. Increases in adrenaline concentration corresponded with increases in tremor amplitude, fall in diastolic BP, and level of HbA_1. There was no correlation between change in adrenaline concentration and duration of diabetes.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">At mild hypoglycemia subjects who recognized a LBG were those with significant increases in circulating adrenaline and features of sympathetic nervous system activation. Impairment in adrenaline response may be common, even in diabetic subjects without autonomic neuropathy and in those who do not complain of hypoglycemia unawareness.</td></tr>
</table>

Table G-42. Clinical Characteristics

—	Age/sex	BMI (kg/m²)	Duration diabetes (yr)	HbA_1 (%)	Cardiovascular tests of autonomic function	Reduced hypoglycaemic symptoms
Non-diabetics						
(8M, 2F)						
Mean (SEM)	22 (3)	22·1 (0·8)	..	..	..	..
Diabetics						
(*"unaware"*)					..	..
Mean (SEM)	37 (4)	22·9 (0·5)	12 (3)	9·0 (0·3)		
1	37M	23·2	12	9·8	Equivocal	No
2	47M	22·9	10	7·8	Equivocal	Yes
3	33M	23·0	22	9·5	Normal	Yes
4	33F	21·3	5	7·0	Normal	Yes
5	18M	20·0	12	9·8	Normal	Yes
6	66M	20·4	33	8·6	Equivocal	No
7	31M	24·8	5	9·0	Equivocal	No
8	37M	25·1	7	9·0	Equivocal	No
9	29M	24·8	3	8·9	Normal	No
10	28M	24·3	12	11·2	Normal	No
11	45F	22·3	8	7·9	Normal	Yes
Diabetics						
(*"aware"*)					..	..
Mean (SEM)	35 (6)	21·5 (1·2)	4 (1)	9·9 (0·6)		
12	30M	18·9	6	9·6	Normal	No
13	47M	24·6	3	10·8	Normal	No
14	41F	21·0	4	11·0	Normal	No
15	21M	21·3	2	8·3	Normal	No

Reference: Lingenfelser T, Overkamp D, Renn W, Hamster W, Boughey J, Eggstein M, Jakober B. Neuropsychobiology 1992 25:161-65														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
			✓											
Research Question	To evaluate cognitive and psychomotor function, hormonal counter regulation, and symptom awareness during severe insulin-induced hypoglycemia in IDDM													
Study Design	Crossover study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	IDDM												
	Exclusion Criteria	Neuropathy; Retinopathy; additional disease; additional medication												
	Study population Characteristics	Males: 4 Females: 6 Age: 38.5 ± 11.2 years Manifestations of diabetes: 10.5± 4.3 years HbA1 9.5 ± 1.1%												
	Generalizability to CMV drivers	Unclear												
Methods	Subjects allowed to have breakfast and morning insulin dose. A glucose clamp was used to maintain BG at predetermined levels. Subjects were administered a battery of seven neuropsychological tests and a standardized questionnaire assessing hypoglycemia symptoms during euglycemia and hypoglycemia. Subjects were blinded to actual BG levels and the order in which they were manipulated.													
Statistical Methods	Results were expressed as mean and SEM. t-tests were used for hormone analysis and the Wilcoxon signed-ranks test was used for assessment of neuropsychological functions and hypoglycemic symptoms. Bonferroni corrections were performed for psychometric tests.													
Quality Assessment	Quality Score=9.13	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	The effect of Hypoglycemia on a variety of cognitive and physiological functions.													
Results	**Counterregulatory Hormones:** Growth hormone exhibited a sharp rise during developing hypoglycemia. Cortisol increase was significant and gradual. Analysis of hypoglycemia awareness and non-awareness groups failed to reveal differences between groups with regard to age, body weight, metabolic control, and duration of the disease. For data see Table G-43 **Neuropsychological tests:** Most patients performed close to mean values of the standardization group during euglycemia, but deteriorated significantly during hypoglycemia. Current subjective condition worsened significantly. For data see Table G-44													
Authors' Comments	There was remarkable neuropsychological deterioration during severe insulin-induced hypoglycemia. It is not clear whether impairment of cognitive and psychomotor functions derived from side-effects of counter regulation or was due to neuroglycopenia.													

Table G-43. Counterregulatory Hormone Response during Euglycemia and Hypoglycemia

Hormones	Euglycaemia	Hypoglycaemia	p value
Growth hormone, pmol/l	166 ± 58	666 ± 163	< 0.05
Cortisol, µg/dl	15.4 ± 3.2	28.4 ± 3.4	< 0.05
Glucagon, pmol/l	28.5 ± 5.6	33.4 ± 7.9	NS

NS = Not significant.

Table G-44. Neuropsychological Performance during Euglycemia and hypoglycemia (age-related scores in comparison with standardization sample, mean = 100, SD = 10, n >1,000)

Subtests	Euglycaemia	Hypoglycaemia	p value
Digit Symbol (DS)	104.0 ± 10.7	97.3 ± 14.8	< 0.05
Digit Connection (DC)	103.2 ± 9.8	98.5 ± 16.4	NS
Aiming Center I (AC I)	96.5 ± 8.8	90.9 ± 4.7	< 0.01
Aiming Center II (AC II)	98.4 ± 11.4	87.6 ± 16.4	< 0.01
Line Tracing Time (LTT)	104.1 ± 8.2	104.5 ± 13.6	NS
Line Tracing Errors (LTE)	88.7 ± 6.6	76.2 ± 6.3	< 0.01
Reaction Time (RT)	101.0 ± 8.5	94.4 ± 6.0	< 0.01

NS = Not significant.

Reference: Herold KC, Polonsky KS, Cohen RM, Levy J, Douglas F. Diabetes July 1985 34:677-85														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To evaluate cortical function via reaction time (RT), subjective symptoms, and counterregulatory hormone response during insulin-induced hypoglycemia in IDDM													
Study Design	Case control study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	T1DM, insulin dependent Healthy												
	Exclusion Criteria	NR												
	Study population Characteristics	Males: 15 (6 Diabetic) Females: 11 (6 Diabetic) Age: 20-35 years of age Manifestations of diabetes: 10.5± 4.3 years HbA1 9.5 ± 1.1%												
	Generalizability to CMV drivers	Unclear												
Methods	Diabetic subjects were admitted to the research clinic the day before the tests and discontinued intermediate-acting insulin, which was replaced with short-acting insulin delivered via a portable infusion pump. BG rate was monitored and adjusted to euglycemia. All subjects began fasting the evening before the tests began. A glucose clamp was used to maintain BG at predetermined levels. After a 20 minute baseline observation period, insulin was infused, with a variable glucose infusion begun at 20 minutes and adjusted to maintain the glucose at approximately 45mg/dL for 30 minutes. After four reaction time measurements were taken, the insulin infusion was discontinued and plasma glucose returned to euglycemia. BG was measured every 5-10 minutes and glucagon, catecholamines, growth hormone, and cortisol were measured at intervals of 10-20 minutes. RT was measured three times at baseline and at 10 minute intervals throughout the experimental period. The same protocol was used during euglycemic and hypoglycemic studies. For the visual RT test subjects lay in front of a black screen with a midline red stimulus and two green 'warning' lights located 8 degrees to either side of the red stimulus. Subjects were instructed to depress a hand-held button as quickly as possible each time the red light was lit. The RT was defined as the time interval between the activation of the red stimulus until the button was depressed. The visual RT test was designed to minimize practice effect, control for the effects of handedness, and increase the reproducibility of the measurements. Autonomic function was evaluated using heart rate variation, ratio of the R-R interval measured during expiration and inspiration of 10 deep breaths, and the ratio of R-R interval of the 30th beat to the 15th beat after starting. Signs and symptoms of hypoglycemia were evaluation through both objective clinical signs and subjective symptoms. Subjects were blinded to actual BG levels and the order in which they were manipulated.													
Statistical Methods	Means ± SEM Paired or single sample *t*-tests Linear regression analysis Repeated measures ANOVA													
Quality Assessment	Quality Score=9.13	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	

Results	Mean Reaction Time: See Table G-45 Change in RT did not correlate with any measure of severity of hypoglycemia. The incremental area under the glucagon concentration curve was significantly reduced in the diabetic group compared with the normal controls. The epinephrine and norepinephrine responses were also reduced in the diabetic subjects. Growth hormone and cortisol responses were not significantly different between groups. Magnitude of the counterregulatory hormone responses did not correlate with change in RT. The maximum prolongation of reaction time was delayed after glucose nadir in six of the eleven controls and four of the seven diabetic subjects who showed significant prolongation of their reaction time during insulin-induced hypoglycemia. Even those subjects whose RT did not change experienced hypoglycemia. Reaction Time (RT) in Euglycemia: Neither group showed significant change in plasma glucose level over time by ANOVA In diabetic subjects, the RT times were significantly longer than the controls. RT measurements were not correlated with glycosylated hemoglobin values, duration of diabetes, age, or sex. RT did not change significantly over time.(Table G-45) Reaction Time (RT) in Hypoglycemia: In the control group, mean RT was significantly longer. Mean response by individual showed considerable variability. In the diabetic group, mean RT increased significantly. Range of individual responses was wide.
Authors' Comments	Both healthy and diabetic subjects experienced variable cortical sensitivity to hypoglycemia. Individual RT responses were not correlated with differences in the severity or duration of hypoglycemia. Clinical manifestations of LBG may depend not only on the absolute BG concentration but on the differences in the cortical sensitivity to hypoglycemia. The effects of hypoglycemia on RT may not temporally coincide with changes in BG.

Table G-45. Responses to insulin-induced hypoglycemia in individual subjects

Subjects	Change in mean glucose (mg/dl)	Rate of glucose fall (mg/dl/min)	Glucose level for development of symptoms (mg/dl)	Change in mean reaction time (ms)
Diabetic				
1	25.9	2.46	27	46.7
2	9.5	2.14	none	248.0
3	19.1	2.50	37	126.7
4	17.1	1.45	38	4.0
5	20.3	1.18	58	77.0
6	39.8	1.25	51	26.1
7	17.3	2.35	42	1.4
8	50.1	1.79	47	54.8
9	16.8	1.17	none	282.0
10	45.3	1.67	48	41.7
11	18.7	2.00	42	0
12	18.7	1.89	48	24.4
Mean ± SEM	24.9 ± 3.7	1.8 ± 0.1	43.8 ± 2.72	74.7 ± 28.2
Control				
1	7.8	2.39	31	413.5
2	28.60	1.13	51	281.9
3	30.1	1.92	50	351.4
4	11.7	2.68	36	0
5	22.5	2.66	41	2.7
6	16.1	2.48	43	15.9
7	30.7	1.58	40	21.8
8	33.8	3.25	33	20.2
9	27.9	1.30	52	18.1
10	24.1	1.57	50	49.9
11	31.2	2.59	41	140.1
12	32.6	2.50	39	53.2
13	29.6	1.80	56	62.5
14	24.4	1.82	40	27.1
Mean ± SEM	25.1 ± 2.2	2.1 ± 0.2	43.07 ± 2.03	103.8 ± 37.4

Changes in mean glucose and reaction time were calculated as the difference between the mean values obtained during the hypoglycemic insulin infusion and during the euglycemic control study. The rate of glucose fall and glucose level for development of symptoms were determined as outlined under METHODS.

Reference: Blackman JD, Towle VL, Sturis J, Lewis GF, Spire-JP, Polonsky KS. Diabetes March 1992 41:392-99														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To evaluate the cognitive disfunction threshold during insulin-induced hypoglycemia in IDDM													
Study Design	Crossover study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	IDDM, poorly controlled Healthy												
	Exclusion Criteria	NR												
	Study population Characteristics	**Healthy Controls:** Males: 5 Females: 5 Mean Age: 26.7 ± 1.9 Mean Weight: 63.4kg ± 3.0kg Mean BMI: 21.6 ± 0.9kg/m^2			**Diabetics:** Males: 6 Females: 8 Mean Age: 29.5 ± 1.6 Mean Weight: 65.6kg ± 2.3kg Mean BMI: 23.8 ± 0.5kg/m^2 Mean HbA1c: 11.0 ± 0.5% Mean duration of disease: 15 ± 2 years								
	Generalizability to CMV drivers	Unclear												
Methods	Subjects were on a weight maintenance diet before the study. All studies were performed at 0800 after a 10-12 hour overnight fast. Diabetic subjects were admitted to the research clinic the day before the tests and discontinued intermediate-acting insulin, which was replaced with short-acting insulin delivered via a portable infusion pump. BG rate was monitored and adjusted to euglycemia. After a 30 minute baseline observation period subjects received a constant insulin infusion, with variable rate infusion of glucose. The experiment began with the clamping of the glucose infusion, with a total of six experimental periods according to the plasma glucose: baseline, euglycemia clamp, 3.5mM clamp, 2.5mM clamp, return to baseline, and post meal. Event-related potential and RT measurements were made three times during the final 30 minutes of each period. To control for practice effects and the effects of fatigue, each subject underwent an additional study on a separate day. The two studies were identical except that during the control study, the glucose was clamped at the basal level. The order of the studies was randomized, and subjects were blinded as to which study was being conducted. BG was measured every 5 minutes and glucagon, catecholamines, growth hormone, and cortisol were measured at intervals of 10 minutes. Signs and symptoms of hypoglycemia were determined at 10 minute intervals. RT was measured three times at baseline and at 10 minute intervals throughout the experimental period. During each of the six experimental periods subjects were required to perform behavioral tasks as tests of cognitive performance. For the visual RT test subjects lay in front of a black screen with a midline red stimulus and two green 'warning' lights located 8 degrees to either side of the red stimulus. Subjects were instructed to depress a hand-held button as quickly as possible each time the red light was lit. The RT was defined as the time interval between the activation of the red stimulus until the button was depressed.													
Statistical Methods	Paired or single sample *t*-tests Repeated measures ANOVA													
Quality Assessment	Quality Score=10.0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	The effect of Hypoglycemia on a variety of cognitive and physiological functions.													

Results	**Glucose Levels(See Table G-46):** Except for the post-prandial period, the BG levels in the control group were not significantly different from the IDDM group. **Event-related Potentials (See Table G-46):** Neither the amplitude nor the latency of the P300 waveform changed significantly during the euglycemic session in control subjects and IDDM patients. The threshold for changes in P300 latency was between 2.5 and 3.5mM for IDDM patients. **Reaction Time (See Table G-46):** RT increased in response to hypoglycemia both groups. **Symptom Scores in Euglycemia:** No symptoms were reported by either group. **Symptom Scores in Hypoglycemia:** No symptoms at baseline, euglycemia, or 3.5mM. At 2.5mM, 11 of 14 IDDM patients reported symptoms. At 2.5mM all control patients reported symptoms. Symptoms disappeared when BG restored to baseline. **Counterregulatory Hormones:** IDDM patients demonstrated a threshold for counterregulatory changes similar to control patients.
Authors' Comments	In both IDDM patients and controls, the threshold for cognitive disfunction as judged by alterations in P300 latency lies between 3.5 and 2.5mM. The consistency of the behavioral tasks indicated that the increases in P300 latency were due to changes in the decision-making process. These findings indicate that poorly controlled patients with IDDM of 15 yr duration do not have cognitive dysfunction at normal glucose levels, and IDDM in itself does not predispose one to higher glycemic threshold for cognitive dysfunction than nondiabetic subjects.

Table G-46. Changes in Visual P300 latency and Reaction Time (RT) during Hypoglycemia Studies in Patients with Insulin-Dependent Diabetes Mellitus (IDDM) and Control Subjects

Time (min)	Glucose (mM)		P300 latency (ms)		Reaction time (ms)	
	Control	IDDM	Control	IDDM	Control	IDDM
0–30	5.2 ± 0.04	5.1 ± 0.06	410 ± 6	403 ± 9	365 ± 7	375 ± 19
70–100	4.9 ± 0.06	5.3 ± 0.06	411 ± 6	407 ± 9	362 ± 9	380 ± 18
145–175	3.3 ± 0.04	3.5 ± 0.04	416 ± 8	421 ± 7	361 ± 10	399 ± 19
220–250	2.6 ± 0.05	2.5 ± 0.02	435 ± 11*	441 ± 10†	413 ± 18‡	425 ± 23†
265–300	5.4 ± 0.20§	5.4 ± 0.10§	459 ± 12‖	430 ± 9*	432 ± 16‖	414 ± 19‡
330–360	7.6 ± 0.30	11.7 ± 0.40	420 ± 7	410 ± 10	375 ± 10	376 ± 19

All other comparisons not significant.
*$P < 0.05$, †$P < 0.001$, ‡$P < 0.01$, ‖$P < 0.0001$, vs. baseline (0–30 min).
§Plasma glucose at 295 min.

Reference: Holmes CS, Koepke KM, Thompson RG. Psychoneuroendocrinology 1986 (11) 3:353-57														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To evaluate the cognitive disfunction threshold during insulin-induced hypoglycemia in IDDM													
Study Design	Crossover study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	T1 IDDM												
	Exclusion Criteria	Overt diabetic neuropathy as manifested by persistent pain, weakness, or neurotrophic injury to extremities.												
	Study population Characteristics	N=24 Males: 100% Mean Age: 21.3 years of age Mean HbA1c: 9.6% Mean duration of disease: 8 years 2 months Mean IQ: 112.6 SD = 1.9 No evidence of retinopathy with reduced visual acuity All subjects had clinically normal ulnar motor and sensory electro-myographic studies													
	Generalizability to CMV drivers	Unclear												
Methods	All studies were performed at 0730 after an overnight fast. Neuropsychological function was assessed at three concentrations of BG which were set and regulated by an automated insulin/glucose infusion system. Each of the three study periods was three hours long: the last ½ hour was used for the neuropsychological testing protocol while glucose concentrations remained stable. The initial 2 ½ hours of each study period were used to establish the desired BG concentration. An array of sensory and motor test was administered to the subjects to evaluate components of sensory, motor, and cognitive processing. Simple motor responding was evaluated by a finger tapping task which provided an analogous but separate measure of motor speed required for the motor speed required for the reaction time tasks. Simple sensory perception was evaluated by tachistoscopic presentation of single letters which were initially viewed for 5 seconds with exposure times lengthened in 5 msec units until correct recognition occurred, with average recognition time of three letters calculated for each study period. Complex sensory/motor functioning was evaluated with a visual RT apparatus which utilized colored lights as stimuli. The RT tasks utilized simple RT (sensory vigilance), Go/No-Go RT (sensory discrimination), and Choice RT (sensory and response discrimination). RT responses (latency and errors) were recorded for 10 test trials which followed 5 practice trials in each condition. Presentation order of tests was randomized within each of the glucose conditions. Both subjects and observers were blinded to glucose sequences during experiments.													
Statistical Methods	Repeated measures ANOVA Pearson product moment correlations													
Quality Assessment	Quality Score=10.0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Results	See Table G-47 Rate of cognitive processing was influenced by glucose levels. Significant treatment effects were found for latency scores from the Go/No-Go RT ($F = 3.12$, $P < 0.05$) and Choice RT ($F = 9.24$, $P < 0.0006$). Performance latencies were increasingly slowed during hypoglycemia as amount of decision-making increased. No treatment effects were found for the RT error scores. Less complex responding was not reactive to glucose treatments. Simple RT and simpler responding on measures of isolated sensory and motor function remained relatively intact across glucose levels. Pearson product moment correlations did not find any relationship between dependent variables and duration of disease or control (HbA_{1c})													
Authors' Comments	The results support the hypothesis that more complex decision-making skills rather than simpler brain mechanisms are disrupted during hypoglycemia. The demonstrated sensitivity of cognitive processing skills to brief disruptions of euglycemia suggests the need to consider acute, as well as traditionally emphasized chronic, impairments associated with deviations in glucose concentrations when planning treatment regimens.													

Table G-47. Mean (and SD) for Each Study Task

Reaction time (RT) tasks (in hundredth seconds)	Blood glucose levels: Control (110 mg/dl)		High (300 mg/dl)		Low (55 mg/dl)	
Simple RT	39.3	(1.5)	40.2	(1.2)	41.9	(1.6)
Go/No-Go Rt	48.1	(1.3)	49.5	(2.1)	52.6	(2.2)
Choice RT	61.5	(2.5)	60.7	(2.0)	69.1	(1.8)
Letter recognition*	3.2	(0.5)	2.5	(0.9)	2.3	(0.7)
Finger tap	69.5	(12.8)	69.9	(9.9)	68.1	(12.5)

*Results were recorded in msecs but are reported here in hundredth seconds to correspond to RT data.

Means which are underlined are not different at $p < 0.05$.

Reference: Holmes CS, Hayford JT, Gonzalez JL, Weydert JA. Diabetes Care March-April 1983 (6) 2:180-85														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To evaluate the cognitive disfunction threshold during euglycemia, hyperglycemia, and insulin-induced hypoglycemia in IDDM													
Study Design	Crossover study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	T1 IDDM												
	Exclusion Criteria	NR												
	Study population Characteristics	N=12 Male: 6 Female: 6 University students (matriculated)												
	Generalizability to CMV drivers	Unclear												
Methods	Subjects were admitted to the Clinical Research Center the day before the study for a history, physical examination, and written informed consent. Routine dietary and insulin regimens were maintained during the day prior to the study. All studies were performed at 0730 after an overnight fast. Routine morning insulin was withheld. BG was set and regulated by an automated insulin/glucose infusion system. Cognitive functions were assessed at three concentrations of BG: 60mg/dL, 110mg/dL, and 300mg/dL, with the sequence of BG concentrations determined by balanced crossover study design. Each study period was 2 hours long, the first 1½ hours used to establish desired BG concentration, and the last ½ hour used for the cognitive testing protocol. Three tasks were used to assess subjects' cognitive performance at different glucose levels: digit supraspan (auditory memory test); matching familiar figures test, delayed reaction time test (visual discrimination skills, attention tasks); Benton Visual Retention Test (visual spatial tasks); and the Nelson Denny Reading Test (academic tasks). Subjects were blinded to specific testing sequence, BG levels, or test performance adequacy. Order of task presentations was randomized to minimize systematic practice effects.													
Statistical Methods	ANOVA Duncan multiple comparisons procedure													
Quality assessment	Quality Score=10.0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	The effect of Hypoglycemia on a variety of cognitive and physiological functions.													
Results	Preliminary multivariate analysis indicated no significant sex-related performance differences, so the data of males and females were combined for the remainder of the analyses. Significant differences were obtained on the reaction time test when both a short and long delay or interstimulus interval was employed. RT performance was slowed at abnormal glucose levels compared with performance at normal levels (Table G-48). Number of mathematical calculations correctly completed was significantly associated with glucose level. Subjects correctly completed an equivalent number of problems at normal and high BG, while fewer problems were correctly completed at low BG. It was determined that this was because subjects attempted to complete fewer problems with low BG (Table G- 49). Attention to and performance on a RT test requiring rapid motor response was slowed at both high and low BG compared with normal levels.													
Authors' Comments	Different glucose levels affect some types of cognitive functioning. There may be some performance impairment during hypoglycemia, but this finding requires further exploration. Immediate memory for digits and words was not impaired during abnormal glucose states. The rate of remembering information may have been impaired at low BG levels, particularly for math facts, but was not impaired for reading comprehension was not impaired (Table G- 50.;Table G-51).													

Table G-48. Mean RT for Short and Long Interstimulus Intervals (in hundredths of a second)

Blood glucose level	Interstimulus interval: Short (2–4 s)	Grouping*	Long (6–8 s)	Grouping*
Low	43.6 (SD = 7.6)	A	46.6 (SD = 92)	A
Normal	39.1 (SD = 5.0)	B	39.7 (SD = 6.3)	B
High	41.8 (SD = 8.5)	A	43.6 (SD = 7.5)	C

*Different letter groupings indicate significant differences among means at the $P < 0.05$ level.

Table G- 49. Mean Number of Mathematical Problems Completed

Blood glucose level	Number correct	Grouping*	Percentage correct	Grouping*
Low	18.9 (SD = 9.0)	B	95.8 (SD = 4.8)	A
Medium	21.5 (SD = 10.5)	A	95.8 (SD = 6.5)	A
High	21.7 (SD = 9.9)	A	98.1 (SD = 3.0)	A

*Different letter groupings indicate significant differences among means at the $P < 0.05$ levels.

Table G- 50. Mean Number of Words Recalled Across Learning Trials

Trial	Blood glucose level: Low	Medium	High
Trial 1	7.2 (1.6)	7.1 (1.7)	7.2 (1.4)
Trial 2	9.8 (2.2)	8.8 (2.1)	9.9 (2.1)
Trial 3	11.8 (2.7)	11.6 (1.9)	12.4 (3.2)
Trial 4	12.4 (2.5)	12.6 (2.1)	12.9 (1.6)
Trial 5	12.8 (2.3)	13.2 (2.0)	12.8 (1.7)
Total (Trials 1–5)	53.8 (8.5)	53.2 (7.5)	55.2 (7.0)

*Total words possible recall = 15/trial. SD are in parentheses.

Table G-51. Mean Number of Reading Comprehension Questions Completed

Blood glucose level	Number correct	Grouping*	Number attempted	Grouping*
Low	7.2 (SD = 2.9)	A	9.2 (SD = 2.3)	A
Medium	6.5 (SD = 2.5)	A	9.0 (SD = 2.0)	A
High	6.8 (SD = 2.4)	A	9.3 (SD = 2.1)	A

*Same letter grouping indicates that means were not significantly different at the $P < 0.05$ level.

Reference: Hoffman RG, Speelman DJ, Hinnen DA, Conley KL, Guthrie RA, Knapp RK. Diabetes Care March 1989 (12) 3:193-97														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		✓												
Research Question	To evaluate cognitive disfunction during insulin-induced hypoglycemia in IDDM													
Study Design	Crossover study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	T1 IDDM												
	Exclusion Criteria	NR												
	Study population Characteristics	N=18 Male: 6 Female: 10 Mean age: 29.3 ± 1.2 Mean duration of diabetes: 7.7 ± 1.6 years Mean age at onset: 21.6 ± 2.0 years Mean HbA1c: 6.9 ± 1.3 No neuropathy or retinopathy													
	Generalizability to CMV drivers	Unclear												
Methods	Subjects were admitted to the Clinical Research Center the day before the study, where BG was set and regulated by an automated insulin/glucose infusion system following an overnight fast. Routine morning insulin was withheld. Cognitive functions were assessed at three concentrations of BG: 50mg/dL, 100mg/dL, and 300mg/dL, according to a pre-assigned order. Each assessment period was ~ 30 minutes, with a 60 – 120 minute interval before testing and between test periods to allow for glucose/insulin regulation and stabilization. Total time to complete the series and reregulation was 8-10 hours per subject. A series of sensory, motor, and cognitive tests of increasing difficulty were administered to each subject at each glucose concentration level. Simple motor speed and RT were assessed using a visually cued reaction timer. Vigilance and motor control were assessed by performance on a pursuit rotor. A trail-making test was administered to assess sensory motor and higher-cortical functioning. 10 of the 18 subjects took part in an assessment of driving performance with an automobile driving simulator. Subjects and investigators were blinded to specific BG adjustment sequence.													
Statistical Methods	Multivariate analysis; repeated measures MANOVA Mean and SE Least significant differences test													
Quality assessment	Quality Score=10.0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	The effect of Hypoglycemia on a variety of cognitive functions.													
Results	Preliminary multivariate analysis indicated no significant sex-related performance differences, so the data of males and females were combined for the remainder of the analyses. Significant main effects for glucose level were seen only for trails B (Table G-53;Table G-54) and pursuit rotor performance (Table G-52). RT was generally slower during hypoglycemia, but considerable variability was seen in RT performance in this condition and the overall effect failed to reach significance. Signaling, braking, and acceleration performance in the driving simulator were also poorer for several subjects but failed to reach statistical significance, with considerable variability noted, and low correlation with duration of disease or HbA1c. Means for the hypoglycemia trials were significantly different at the P ≤ 0.01 level from those at normoglycemia and hyperglycemia, with performance poorer during hypoglycemia. 25% of subjects performed at the level of mild to serious impairment in the hypoglycemia condition, whereas all subjects performed in the normal range in the normoglycemia and hyperglycemia conditions.													
Authors' Comments	This study suggested reversible decrements in cognitive functioning at BG levels of ~ 50mg/dL, particularly on novel tasks requiring sustained concentration and decision making. Cognitive impairment may therefore occur before patients are aware that they are hypoglycemic and before subjective symptoms of confusion or concentration difficulties generally occur.													

Table G-52. Pursuit Rotor Performance

Blood glucose level	Time (s)
Hypoglycemia	14.38 ± 9.49*
Normoglycemia	22.88 ± 11.76
Hyperglycemia	20.13 ± 9.77

Values are means ± SD of seconds per 1-min trial.
*$P < .01$, significantly different from normoglycemia and hyperglycemia.

Table G-53. Trail making Tests parts A and B

Blood glucose level	Time (s)
Trails A	
Hypoglycemia	24.34 ± 5.88
Normoglycemia	23.43 ± 7.53
Hyperglycemia	21.37 ± 4.35
Trails B	
Hypoglycemia	66.99 ± 25.74*
Normoglycemia	49.61 ± 20.41
Hyperglycemia	50.20 ± 12.08

Values are means ± SD of seconds per 1-min trial.
*$P < .01$, significantly different from normoglycemia and hyperglycemia.

Table G-54. Percentage of Subjects in Halstead-Reitan Impairment Ranges for Trails B

	Perfectly normal (0–60 s)	Normal (61–72 s)	Mildly impaired (73–105 s)	Seriously impaired (106+ s)
Hypoglycemia (%)	56.3	18.7	12.5	12.5
Normoglycemia (%)	88.2	11.8	0	0
Hyperglycemia (%)	82.4	17.6	0	0

Study Summary Tables (Key Question 3)

No studies met the inclusion criteria for this Key Question.

Study Summary Tables (Key Question 4)

<table>
<tr><td colspan="15">Reference: Cox DJ, Kovatchev B, Koev D, Koeva L, Dachev S, Tcharaktchiev D, Protopopova A, Gonder-Frederick L, Clarke W. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int J Behav Med 2004;11(4):212-8.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="7">4</td></tr>
<tr><td></td><td colspan="3"></td><td colspan="3"></td><td colspan="7">✓</td></tr>
<tr><td>Research Question</td><td colspan="14">Compared to self-monitoring of blood glucose levels, is HAATT(now referred to as BGATHome) effective in reducing the risk for hypoglycemia among Bulgarians with type I diabetes?</td></tr>
<tr><td>Study Design</td><td colspan="14">Multicenter (3 centers) RCT</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">1</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Type I diabetes; ≥2 episodes of severe hypoglycemia (hypoglycemia requiring assistance from a third party)</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">All type I diabetics; see Table G-55 below.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Adults with type 1 Diabetes Mellitus (T1DM) and a history of ≥2 episodes of severe hypoglycemia (SH, defined as inability to treat oneself due to hypoglycemic stupor or unconsciousness) in the past year were recruited via direct physician referral at routine patient visits. Participants each given an Accu-Chek Easy Meter, 4 months of supplies (1 month pre-treatment, 2 months treatment, 1 month post-treatment), instruction on meter use and data interpretation, and $20 for data collection.
For six months prior to treatment, participants delivered monthly diaries detailing any episode of moderate hypoglycemia (MH, defined as neuroglycopenia to the point where participant could not continue normal activities, but did not preclude self-treatment) or SH to their physician. For the final month prior to treatment patients were given SMBG equipment and supplies and daily diaries. Daily diary entries were made q.i.d. and detailed the following: estimation of whether BG was hypoglycemic, euglycemic, or hyperglycemia as defined by BG levels of <3.9, 3.9-10, and >10mmol/L; report (yes or no) hypoglycemic symptoms at that time; measure and record actual BG; decide, based on their BG, whether patient would eat nothing, have a sweet drink, or food at that time.
Based on the monthly diaries, participants were matched on hypoglycemia occurrence and demographic variables and randomly assigned to either HAATT or SMBG groups. All participants received routine medical care (involving regular physician visits to make adjustments in insulin, food, and exercise routine based on the daily SMBG data).
SMBG group: During the treatment phase participants received Accu-Chek equipment and supplies and education on the meaning and use of SMBG data
HAATT group: During the treatment phase participants received Accu-Chek equipment and supplies and a structured, 7 week-group psychoeducational treatment program. The psychoeducational treatment program consisted of weekly readings of the program manual, group sessions to discuss the chapter content, and daily homework exercises based on the readings. The homework consisted of completing daily records immediately before SMBG measurements, including considering content of the assigned reading, writing down insulin action, carbohydrates ingested, physical exercise performed, symptoms experienced. Based on this information, HAATT participants wold then estimate, then measure and record actual BG levels. If this level was <3.9 mmol/L, subjects were to record additional information about causes and treatment of this low BG event. Homework assignments were reviewed at the next class.
For the first month of the post-treatment phase participants completed daily diary entries four times a day. For months one to six post-treatment participants continued to record MH and SH incidences. For months 13-18 post-treatment participants completed monthly diaries, recording MH and SH incidences.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Frequency of MH and SH and nocturnal hypoglycemia determined. The following measures were employed in 2 (pre- vs. post-) x 2(HAATT vs. SMBG) ANOVA with the primary factor of interest being the interaction term: estimated HbA_{1C} based on 1 month of SMBG data; Average actual BG, BG standard deviation, minimum and maximum BG; BG Risk Index, Low BG Risk Index and High BG Risk Index; percent of time when hypoglycemic symptoms reported at BG <3.9mmol/L; percent detection of Low BG by calculating percentage of time participant estimated his or her BG to be below 3.9 mmol/L when it actually was below 3.9mmol/L; Overall accuracy of BG evaluation, percent recognition of hypoglycemia, euglycemia, and hyperglycemia; and percent appropriate treatment decisions calculated as a percentage of time when participant decided to treat low BG with sweet drinks. T tests were used to compare the HAATT and SMBG MH, SH, and nocturnal hypoglycemia events during months 13-18. Treatment effects were assessed first in terms of the month of daily diary data pre- and post- treatment, then in terms of the monthly diaries collected for 3 months pre-, post-, and follow-up.</td></tr>
<tr><td rowspan="3">Quality assessment</td><td rowspan="2">Quality Score=6.2</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>NR</td><td>Y</td><td>NR</td><td>N</td><td>NR</td></tr>
<tr><td>Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
</table>

		NR	NR	NR	NR	Y	Y	Y	Y	Y	Y	N	Y	
Relevant Outcomes Assessed	Difference in frequency and extent of low blood glucose events Difference in reduction in significant hypoglycemia Difference in reduction in extreme fluctuations in blood glucose levels Difference in low blood glucose detection, symptoms, and appropriateness of treatment													
Results	Primary followup time (6 months): Patients treated with HAATT demonstrated significant reductions in frequency and extent of low blood glucose events; reductions in extreme blood glucose level fluctuations, and better recognition of hypoglycemia accompanied by corrective action (see Table G-56). Longer term followup (13-18 months): Patients who received HAATT experienced fewer hypoglycemic episodes of severe hypoglycemia (1.76 vs 5.26; F=10.68 (df=54); P <0.01).													
Authors' Comments	The overall benefits of HAATT were maintained at 13 to 18 month follow-up, suggesting robust benefits. The multicenter approach to this research also suggested that the benefits may be generalizable across populations.													

Table G-55. Baseline Characteristics of Enrolled Patients

	All (N = 60)	HAATT (N = 30)	Control (N = 30)	P-value
Age (years)	38.06 (9.27)	37.60 (9.00)	38.62 (9.76)	0.69
Percent male	53%	53%	54%	> 0.92
Percent married	80%	83%	76%	0.70
Education (years)	13.10 (2.47)	13.14 (2.37)	13.04 (2.66)	> 0.90
Body mass index	23.17 (3.26)	23.61 (3.44)	22.63 (2.99)	0.27
Diabetes duration (years)	13.96 (8.53)	13.93 (9.33)	14.00 (7.64)	> 0.98
HbA1c[a]	8.04 (0.71)	8.08 (0.74)	7.98 (0.70)	> 0.94
Insulin units per day	44.75 (14.13)	46.63 (14.91)	42.30 (12.96)	0.26
Insulin Injections per day	3.09 (1.06)	3.20 (1.12)	2.96 (0.98)	0.41

Note. [a]HbA1c estimated based on an algorithm applied to baseline SMBG records.

Table G-56. Results Reported

Outcome Variables	HAATT Pre-Post	SMBG Pre-Post	Interaction Effect F value	Interaction Effect p value
A: Reduction in frequency and extent of low BG events (daily diaries)				
Low BG index	3.9 to 2.8	4.5 to 7.4	9.7	.003
Percent of BGs < 3.9	15.6 to 11.7%	17.1 to 18.5%	4.9	.03
Mean minimum BG/subject (mmol/L)	2.1 to 2.4	2.1 to 1.7	6.6	.013
B: Reduction in significant hypoglycemia (monthly diaries)				
Severe hypoglycemia/subject	2.0 to 0.4	1.8 to 1.7	5.0	.03
Moderate hypoglycemia/subject	8.7 to 5.3	9.7 to 11.0	35.5	< .001
Nocturnal hypoglycemia/subject	1.1 to 0.8	0.6 to 1.6	3.9	.055
C: No compromise in blood glucose control (daily diaries)				
HbA1c[a]	8.1 to 8.0	8.0 to 8.1	0.3	*ns*
Average BG (mmol/L)	9.5 to 9.3	9.3 to 9.1	.02	*ns*
Mean maximum BG/subject (mmol/L)	23.3 to 19.7	20.3 to 20.8	1.4	*ns*
High BG Index	11.5 to 10.0	11.0 to 10.6	0.4	*ns*
D: Reduction in extreme BG fluctuations (daily diaries)				
BG risk index	15.5 to 12.8	15.5 to 17.9	7.0	.01
Standard deviation of BG (mmol/L)	4.90 to 4.05	4.71 to 4.74	5.96	.018
Percent Accuracy of BG evaluation	67 to 82%	75 to 73%	19.3	< .001
E: Low BG detection, symptoms, and appropriateness of treatment (daily diaries)				
Percent Detection of low BG	52 to 70%	58 to 55%	8.4	.005
Percent Low BGs accompanied by symptoms	60 to 70%	56 to 58%	0.4	*ns*
Percent Decision to treat with sweet drink[b]	58 to 71%	52 to 58%	.60	*ns*

[a]HbA1c estimated based on an algorithm applied to baseline SMBG records [b]Pre-post effect p = 0.03.

<table>
<tr><td colspan="15">Reference: Schachinger H, Hegar K, Hermanns N, Straumann M, Keller U, Fehm-Wolfsdorf G, Berger W, Cox D. Randomized controlled clinical trial of blood glucose awareness training (BGAT III) in Switzerland and Germany. J Behav Med 2005;28(6):587-94.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="6">4</td></tr>
<tr><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td><td colspan="6">✓</td></tr>
<tr><td>Research Question</td><td colspan="14">Compared to self-monitoring of blood glucose levels, is HAATT(now referred to as BGATHome) effective in reducing the risk for hypoglycemia among Europeans (Swiss and Germans) with type I diabetes?</td></tr>
<tr><td>Study Design</td><td colspan="14">RCT, multicenter</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">1</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Diabetes.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Uncontrolled physical disease (ex. Coronary or vascular disease) and/or mental disease (depression, eating disorder, substance abuse). Comorbidity was considered uncontrolled when newly diagnosed or new treatment had to be established within the last 3 months prior to supposed study entry.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">All subjects were on an intensified insulin regimen, performed three to five injections per day and at least three BG measurements per day, had a recent adjustment to insulin dose and dosing schedule (if necessary), and routine determination of HbA_{IC} every three months (See Table 1)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">168 participants went through a 6 month baseline assessment period, after which they were randomly assigned to either BGAT (treatment) or a physician-guided self-help group (control). Subjects were matched to controls for approximate age and duration of diabetes. Each study center had at least one treatment and control intervention offered.
BGAT III was delivered by a physician-psychologist team to groups of five to twelve subjects in eight weekly sessions. Weekly homework and preparatory readings were required.
The self-help group was guided by a physician. Five to twelve subjects participated in three monthly sessions. Each session lasted about 2 hours. There was no homework assigned.
All participants were instructed to use a two month diary. Information to be noted in the diary included: date and time of BG measurement; BG estimation; actual BG values, and remarks. Participants tested BG at least three times daily; most tested four times a day (fasting BG, pre-prandial BG, and before bed BG). SH was assessed using diary BG data and as questionnaires at six and twelve months.
A minimum of three consecutive weeks with complete data pairs of BG measurements was necessary for each individual participant and assessment point for the participant to be included in the analyses. BG accuracy index, detection of low (<4mmol/L) and high (>10mmol/L) BG and low and high BG risk index were calculated according to published standards. BG thresholds for hypoglycemia symptoms were reported by the subjects based on regular self monitoring BG, representing subjective measurements.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">A repeated measures ANOVA was used to examine the impact of treatment and time.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score=0.51</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>Y</td><td>NR</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Glycosylated hemoglobin (HbA_{IC}) was determined by an immuno-enzymatic method.
Difference in frequency and extent of low blood glucose events
Difference in reduction in significant hypoglycemia
Difference in low blood glucose detection, symptoms, and appropriateness of treatment
Standardized questionnaires were used to assess diabetes specific locus of control and diabetes specific and general QOL measures.
Diabetes specific locus of control questions measured four distinct scales: internalization, externalization, unpredictability, and chance control.
The Bradley Well-Being Questionnaire was used to assess depression, anxiety, positive well-being, and perceived energy over the previous seven days.
The Diabetes Quality-of-Life questionnaire measured satisfaction, impact, and diabetes-related worry.
A 19 item mood questionnaire (in German only) was employed to measure fatigue, hopelessness, negative mood, and positive mood. Validation studies revealed internal consistencies between 0.83 and 0.94.
The Hypoglycemia Fear Survey, based on reactions to severe hypoglycemia episodes, measured worry and behavior scales.</td></tr>
</table>

Results	Incidence of motor vehicle accidents, hospitalization, and diabetic ketoacidosis was low in both BGAT and control groups at Baseline (See Table G-57). BGAT led to a decrease in SH episodes and increased recognition of low BG and high BG levels, with improvement in the BG accuracy index and subjective recognition for hypoglycemic symptoms (see Table G-58). Extreme BG fluctuations and HbA_{1C} were not influenced by treatment (see Table G-58). Locus of control became less external and unpredictability decreased for treatment group participants related to diabetes. (See Table G-58)
Authors' Comments	The study demonstrates BGAT's efficacy in reducing SH without compromising metabolic control in European settings. The study also demonstrates BGAT's efficacy in achieving improved recognition of low BG and high BG, and reduced external locus of control. Results of this study are in accordance with previous findings in USA T1DM samples.

Table G-57. Baseline Patient Characteristics

Variable	BGAT (n=56)	Control (n=55)	Drop-outs (n=27)
Sex (female/male)	25/31	21/34	12/15
Age (years)	45 (14.4)	47.9 (13.1)	48.1 (13.4)
Diabetes duration (years)	23.1 (12)	22.7 (12.2)	22.5 (13.9)
BMI (kg/m2)	24.5(4.5)	23.4 (3.5)	24.2 (4.1)
During last 2 years before study			
Patients with SH (%)	64	47	50
Patients with hypoglycemia coma	28	25	33
During last 6 months before study			
Motor vehicle accidents (n)	2	2	0
Hospitalization (n)	5	6	7
Diabetic ketoacidosis (n)	0	1	1

Table G-58. Findings

Variable	T0	T1	T2	Time x Group Interaction	Contrast T1 vs T0 group effect	Contrast T2 vs T0 group effect
Severe hypoglycemia (episodes/6 months)						
BGAT (n=56)	1.61 (3.49)	0.13 (0.33)	0.13 (0.33)	*F* (2,218) = 3.14 P=0.04	*F* (1,169) = 1.73 P=0.19	*F* (1,109) = 4.04 P=0.04
Control (n=55)	1.76 (3.71)	1.07 (2.85)	1.78 (4.56)			
Percent detection of LBG levels						
BGAT (n=33)	52.7 (21.8)	58.2 (24.8)	65.2 (25.2)	*F* (2,132) = 4.92 P=0.008	*F* (1,66) = 3.79 P=0.05	*F* (1,66) = 8.39 P=0.005
Control (n=35)	53.5 (28.0)	45.8 (28.7)	48.0 (25.5)			
Percent detection of HBG levels						
BGAT (n=33)	45.0 (23.6)	53.1 (25.1)	53.7 (26.2)	*F* (2,126) = 3.54 P=0.63	*F* (1,63) = 5.93 P=0.02	*F* (1,63) = 2.62 P=0.11
Control (n=32)	38.8 (24.0)	33.5 (25.8)	38.2 (23.5)			
Accuracy Index						
BGAT (n=37)	38.8 (17.1)	45.1 (21.6)	47.3 (21.7)	*F* (2.144) = 7.04 P=0.001	*F* (1.72) = 5.21 P=0.02	*F* (1.72) = 11.37 P=0.001
Control (n=37)	38.5 (17.5)	35.9 (18.5)	34.6 (19.5)			
Subjective Hypoglycemia symptom threshold						
BGAT (n=44)	3.08 (0.73)	3.38 (0.64)	3.30 (0.72)	*F* (2.178) = 2.97 P=0.05	*F* (1.89) = 5.10 P=0.02	*F* (1.89) = 1.45 P=0.23
Control (n=47)	3.25 (0.83)	3.29 (0.75)	3.34 (0.70)			
Low BG index						
BGAT (n=43)	2.99 (1.54)	2.48 (1.34)	2.61 (1.32)	*F* (2.176) = 0.52 P=0.60	*F* (1.83) = 0.76 P=0.39	*F* (1.85) = 0.67 P=0.42
Control (n=44)	2.62 (1.43)	2.53 (1.44)	2.49 (1.73)			
High BG index						
BGAT (n=43)	6.53 (3.29)	6.64 (3.37)	6.29 (2.82)	*F* (2.176) = 0.77 P=0.46	*F* (1.85) = 11.00 P=0.99	*F* (1.85) = 1.08 P=0.36
Control (n=44)	5.85 (2.92)	5.95 (3.64)	6.17 (3.35)			
Glycosylated Hemoglobin						
BGAT (n=53)	6.93 (0.82)	6.93 (1.02)	6.93 (0.96)	*F* (2.202) = 0.06 P=0.94	*F* (1.101) = 0.09 P=0.76	*F* (1.101) = 0.03 P=0.85
Control (n=50)	6.91 (0.94)	6.95 (0.94)	6.94 (0.94)			

Table G-59. Locus of Control

Variable	T0	T1	Time x group interaction
Locus of Control			
Internalization			
BGAT (n=54)	38.9 (6.6)	38.6 (7.1)	*F* (1.101) = 0.00 *P*=0.96
Control (n=49)	38.4 (6.4)	38.1 (6.6)	
Externalization			
BGAT (n=54)	22.4 (7.8)	26.4 (8.0)	*F* (1.101) = 5.43 *P*=0.02
Control (n=49)	19.5 (8.4)	19.8 (8.6)	
Chance control			
BGAT (n=54)	9.2 (4.6)	8.8 (4.4)	*F* (1.101) = 0.40 *P*=0.75
Control (n=49)	9.5 (4.9)	9.4 (5.2)	
Unpredictability			
BGAT (n=54)	27.9 (8.2)	24.1 (8.1)	*F* (1.101) = 14.6 *P*=0.0002
Control (n=49)	26.5 (8.4)	27.2 (8.9)	

<table>
<tr><td colspan="5">Reference: Broers S, le Cessie S, van Vliet KP, Spinhoven P, van der Ven NC, Radder JK. Blood Glucose Awareness Training in Dutch Type 1 diabetes patients. Short-term evaluation of individual and group training. Diabet Med 2002 Feb;19(2):157-61.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td></td><td></td><td></td><td>✓</td></tr>
<tr><td>Research Question</td><td colspan="4">To assess the effect of BGAT (group or individual) one year after training on handheld computer measures of BG perception, decisions not to drive and to raise the BG during hypoglycemia; diabetes regulation; and on measures of hypoglycemia related worry, severe SH, and self-monitoring of BG.</td></tr>
<tr><td>Study Design</td><td colspan="4">Controlled trial</td></tr>
<tr><td>USPSTF Level</td><td colspan="4">1</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="3">Type 1 Diabetes.
Diagnosed with T1DM before 40 years of age and at least two years prior to invitation to participate in study
Used multiple insulin injections daily or CSII (continuous subcutaneous insulin infusion)
Under 65 years of age</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="3">No serious physical or psychological comorbidity (comorbidity not detailed)</td></tr>
<tr><td>Study population Characteristics</td><td colspan="3">All Type 1 diabetics; See Table G-60 below.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="3">Unclear</td></tr>
<tr><td>Methods</td><td colspan="4">123 individuals with type 1 Diabetes mellitus invited to take part in research project on reduced hypoglycemic awareness. Participants given opportunity to choose their study group; no BGAT training (control), Group BGAT training (treatment group 1a) or individual BGAT training (treatment group 1b).
Note: Individuals who chose the ‘no BGAT training’ group were not enumerated in this study.
Group BGAT participants met in groups of five to nine individuals with a diabetes educator and a psychologist for six weekly 1.5 – 2 hour sessions.
Individual BGAT participants met in six 30-minute sessions with a diabetes educator.
All participants interviewed at the hospital, completed questionnaires, and had blood drawn for HbA_{1C} assessment. Participants performed up to 70 handheld computer (HHC, Psion P-250, Hoofddorp, the Netherlands) BG measurements at home (b.i.d. – q.i.d.) over a four to six week period. Participants performed the BG measurements when they habitually checked their BG, and when they expected BG to be high or low. For each HHC measurement, participants were instructed to estimate whether they would raise their BG and whether they would participate in traffic on the basis of their estimation, and then determined their BG level. Each participant was loaned a One Touch Profile BG memory meter (Lifescan, Beerse, Belgium).
After BGAT training, participants performed HHC measurements. One year after BGAT training, participants performed HHC measurements and completed questionnaires.</td></tr>
<tr><td>Statistical Methods</td><td colspan="4">Descriptive statistics and frequencies used to describe sample.
Non-parametric test used for SMBG variable, as this variable not normally distributed.
T-tests and X_2 tests used to assess the differences between participants vs nonparticipants and participants in BGAT groups vs. participants in individual BGAT training.
Repeated measures analysis used to assess significance of change over time and possible differential effect of group BGAT vs. individual BGAT treatment.
Paired t-tests used for post-hoc comparisons when time x treatment interaction was significant</td></tr>
<tr><td>Quality assessment</td><td colspan="4"><table>
<tr><td rowspan="2">Quality Score=0.33</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>N</td><td>N</td><td>N</td><td>N</td><td>N</td><td>Y</td><td>NR</td><td>N</td><td>Y</td><td>N</td></tr>
<tr><td rowspan="2">Unacceptably Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td></td></tr>
</table></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="4">Difference in frequency and extent of low blood glucose events
Difference in reduction in significant hypoglycemia
Difference in low blood glucose detection, symptoms, and appropriateness of treatment
Difference in judgement to drive during hypoglycemia</td></tr>
<tr><td>Results</td><td colspan="4">Differences between objective measures of hypoglycemic awareness were not significant (Table G-61).
After BGAT, the percentage of recognized hypoglycemic episodes, decisions not to drive during hypoglycemia, and decisions to raise BG during hypoglycemia improved (Table G-61)
Changes in scores after group and individual BGAT treatment differed significantly for two measures: accuracy index (P=0.04) and HBG index (P=0.03), with post-hoc comparisons demonstrating that the accuracy index improved after group BGAT, but not after individual BGAT.
After BGAT training, the number of reported SH episodes decreased (P=0.001), participants performed BG self-monitoring more often (P=0.000), and were involved in traffic accidents less often (P=0.04) (Table G-62).</td></tr>
<tr><td>Authors’Comments</td><td colspan="4">There were significant improvements in clinically relevant measures one year after BGAT. Group BGAT training should be preferred over individual BGAT training, but individual training also improved hypoglycemic awareness.</td></tr>
</table>

Table G-60. Baseline Characteristics

	No training (N=64)[a]	Group BGAT (N=37)	Individual BGAT (N=22)	*P*= (Training *vs.* No training[b])	*P*= (Group *vs.* Individual[b])
Age (years)	39.3 (11.8)	43.7 (9.2)	42.5 (11.1)	0.05	0.65
Gender	45% male	68% male	50% male	0.08	0.18
Education[c]	5.1 (2.2)	5.6 (1.9)	4.8 (2.1)	0.74	0.14
Duration of DM (years)	20.2 (10.9)	23.9 (9.4)	21.3 (12.1)	0.17	0.36
HbA1c (%)	7.9 (1.4)	7.5 (1.4)	7.5 (1.0)	0.11	0.93
Neuropathy[d]	1.4 (1.7)	1.4 (1.8)	1.3 (1.4)	0.86	0.84
CSII	6%	11%	5%	0.64	0.40
Hypo awareness 0-10[e]	6.4 (2.8)	4.0 (2.4)	5.2 (2.7)	0.00	0.09
BG level of detecting hypo[e]	3.7 (1.0)	2.7 (1.0)	2.7 (0.8)	0.00	0.97
Accuracy index[f]	19.0 (22.5)	7.7 (15.4)	13.1 (16.2)	0.01	0.21
Recognized hypoglycaemia[f] (%)	45.6 (31.0)	31.7 (22.8)	34.8 (25.6)	0.03	0.67
No. of severe hypos last year[e]	3.0 (6.2)	6.6 (7.0)	6.6 (6.9)	0.03	0.98

[a] Participants who did not receive blood glucose awareness training (BGAT) were not included in the present study (see discussion).
[b] Significance of independent sample t-test, except for gender and CSII: significance of _2 test.
[c] Educational level ranged from 1 (primary school) to 8 (university).
[d] Three cardiovascular function tests were used: heart rate response to standing up, heart rate response to deep breathing and blood pressure response to standing up.14 A higher score reflects more severe autonomic neuropathy.
[e] Self-report.14 handheld computer data.

Table G-61. Handheld Computer Scores and HbA_{1c} before and after BGAT

	Group BGAT (N=24)		Individual BGAT (N=12)		*P*= (time)	*P*= (Interaction)	N
	Baseline	Followup	Baseline	Followup			
Accuracy index (%)	5.3 (15.2)	18.8 (18.9)	13.6 (11.7)	11.7 (10.6)	0.12	0.04	36
Recognized hypoglycemic episodes (%)	27.9 (24.6)	42.1 (23.7)	35.3 (33.7)	42.4 (25.6)	0.02	0.40	34[a]
Recognized hyperglycemic episodes (%)	33.9 (23.4)	38.9 (27.5)	40.1 (20.0)	39.8 (18.7)	0.55	0.49	36
HbA1c (%)	7.3 (1.2)	7.3 (1.3)	7.2 (0.9)	7.5 (1.1)	0.30	0.22	44
Low blood glucose index	[b]3.8 (1.4)	4.2 (3.0)	4.1 (2.7)	3.1 (1.8)	0.61	0.15	36
High blood glucose index	10.7 (4.8)	9.9 (6.4)	11.4 (4.6)	13.4 (7.1)	0.33	0.03	36
Blood glucose risk index	14.5 (4.6)	14.1 (5.8)	15.5 (3.7)	16.5 (6.3)	0.61	0.31	36
Not driving during hypoglycemia (%)	43.5 (29.7)	57.8 (27.8)	36.1 (29.8)	47.2 (27.1)	0.01	0.73	35[b]
Raising BG during hypoglycemia (%)	51.3 (29.7)	64.3 (33.5)	41.5 (31.1)	54.9 (27.9)	0.02	0.98	35

Significance of change after BGAT ('time') and significance of the difference in effect of the treatment conditions ('interaction').

[a] Two patients measured less than two hypoglycemic episodes.
[b] One patient did not measure any hypoglycemic episodes.

Table G-62. Mean Questionnaire Scores at Baseline and at 1-Year Followup

	Group BGAT		Individual BGAT		*P*= (time)	P= (Interaction)	N[a]
	Baseline	Followup	Baseline	Followup			
HFS worry[b]	20.2 (11.3)	18.9 (10.1)	19.4 (11.3)	17.9 (11.9)	0.29	0.95	46
Severe hypoglycemia[c]	7.9 (7.5)	1.7 (2.4)	6.6 (7.6)	0.3 (8.5)	0.001	0.26	26
SMBG[d]	2.4 (2.0)	3.2 (1.7)	2.4 (1.5)	3.7 (1.6)	0.000	0.28	49
Traffic accidents[e]	0.3 (0.4)	0.1 (0.4)	0.6 (0.5)	0.2 (0.4)	0.04	0.32	33

Significance of change after BGAT ('time') and differential effect of the treatment conditions ('interaction').

[a] 49 patients returned questionnaires, smaller n's are the result of missing data.

[b] HFS=hypoglycemia fear survey.

[c] Number of reported severe hypoglycaemic episodes per year.

[d] SMBG=times a day of self-monitoring of blood glucose.

[e] Number of reported traffic accidents per year

<table>
<tr><td colspan="15">Reference: Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes Care 2001 Apr;24(4):637-42.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="2">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="6">4</td></tr>
<tr><td colspan="2"></td><td colspan="3"></td><td colspan="3"></td><td colspan="6">✓</td></tr>
<tr><td>Research Question</td><td colspan="14">To investigate the long-term (12-month) benefits of BGAT-2 when compared to</td></tr>
<tr><td>Study Design</td><td colspan="14">Pre-Post study</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-3</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">T1DM for ≥2 years. Insulin use since diagnosis. Routinely take BG ≥ b.i.d.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">History of severe depression or substance abuse.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">All T1DM. At 12 month follow-up there were 25 male and 48 female (N=73) participants.
Mean age=38.3 years old (± 9.1 years). Duration of disease=19.5 years (± 10.5 years).
Insulin U/day=38.9 (± 16.5). HbA_1=10.2 (± 2.1%).</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13"></td></tr>
<tr><td>Methods</td><td colspan="14">Participants used handheld computers (HHC) to estimate BG level, then recorded whether they would raise or lower their BG, and whether they would or would not drive. Participants then measured and recorded actual BG levels. Measurements were taken just before routine SMBG and whenever the participant believed their BG to be high or low. This process was repeated 50 times over a 3 week period.
Participants completed monthly diaries chronicling occurrence of DKA, SH, and motor vehicle violation citations. The diaries were begun 6 months before BGAT training and continued for 12 months after BGAT training.
Participants had blood drawn to measure HbA_1
Repeated baseline design was used to establish stability of measures.
BGAT training was delivered to groups of 5-15 participants in 8 weekly sessions.
Post-BGAT, subjects were matched based on their ability to detect low BG levels and then randomized to either booster or no-booster training. Participants randomized to booster training received prompts to look for BG cues and anticipate high and low BG levels, along with key concept summary pages from the BGAT-2 manual at months 3 and 9; received a summary report concerning HHC results at months 4 and 10; and used BGAT-2 diaries to complete daily for 1 week at months 5 and 11.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Pre-treatment stability assessed using Student's t-test (6 months prior vs Baseline. Multiple analyses of variance (MANOVAs) first performed to test hypotheses concerning long-term effects of BGAT-2 (6- to 1-month pretreatment, 1- to 6-month and 7- to 12-month follow-up) for the separate clusters of dependent variables (BG estimation accuracy, judgment, negative clinical sequelae, and psychological parameters).
Across-subject repeated-measure analyses of variance (ANOVAs) used to assess impact of BGAT-2 on individual variables. When significant (P=0.01) time effects identified, two contrasts performed. Contrast 1 compared 6-month baseline with 6- and 12-month follow-up data to determine whether there was a long-term benefit of BGAT-2. Contrast 2 compared posttreatment with 6- and 12-month follow-up data to assess stability of effect. ANOVAs performed to assess effects of booster training.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality score=5.7</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>NR</td></tr>
<tr><td rowspan="2">Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Difference in frequency and extent of low blood glucose events
Difference in reduction in significant hypoglycemia
Difference in low blood glucose detection, symptoms, and appropriateness of treatment
Difference in judgement to drive during hypoglycemia</td></tr>
<tr><td>Results</td><td colspan="14">Ability of participants to estimate BG levels was significantly improved by BGAT-2, including providing stable and clinically accurate estimates from baseline through 12 months of follow-up.
There was a significant reduction in extreme BG levels from baseline through 12 months of follow-up.
Determination of when to treat high and low BG levels and whether to drive a motor vehicle was significantly improved by BGAT-2 from baseline through 12 months of follow-up
Negative sequelae of extreme BG levels was significantly reduced from baseline through 12 months of follow-up (See Table G-64)</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The data indicate that BGAT-2 has significant, sustained and broad-ranging benefits in the T1DM population. However, the improvement in detection of hypo- and hyperglycemia was modest, and did not correlate with reduction of SH or motor vehicle violations. Results suggest that changes in decision-making and attitude may be just as important as improvements in BG detection. BGAT may be particularly beneficial to patients who are attempting intensive insulin therapy, experience frequent DKA, have had SH or diabetes related car accidents, experience wide fluctuations in BG, or have impaired hypoglycemia awareness.</td></tr>
</table>

Table G-63. Pre-Treatment Outcomes (6 and 1 month prior to BGAT)

Variable	6-and 1-month pre-BGAT	Correlations	Contrasts
Improved recognition of BG levels*			
% Detection of low BG	36±32; 34±31	*F*=0.64, *P*=0.001	*t*=0.9, NS
% Detection of high BG	52±25; 49±26	*F*=0.65, *P*=0.001	*t*=1.1, NS
% Accurate estimates	39±13; 38±13	*F*=0.72, *P*=0.001	*t*=0.1, NS
Reduced extreme BG fluctuations†			
BG risk index	14.1±5.1; 13.7±4.9	*F*=0.55, *P* 0.001	*t*=0.7, NS
HbA1	10.2±2.1; 10.2±2.0	*F*=0.85, *P*=0.001	*t*=0.5, NS
Improved judgement‡			
% Decision to treat when low	49±30; 55±33	*F*=0.34, *P*=0.003	*t*=1.3, NS
% Decision not to drive when low	52±38; 47±38	*F*=0.50, *P*=0.002	*t*=0.8, NS
Reduction of negative consequences§			
DKA (total no.)	4; 3	—	—
Severe hypoglycemia	1.4±2.1; 1.8±1.9	*F*=0.77, *P*=0.001	*t*=1.7, NS
Motor vehicle violations	0.1±0.3; 0.08±0.2	*F*=0.45, *P*=0.001	*t*=0.2, NS
Change in psychological parameters‖			
Hypoglycemia fear survey–worry	23.7±10.3; 20.2±10.1	*F*=0.76, *P*=0.001	*t*=4.3, *P*=0.01
DQOL–impact	46.7±10.5; 45.8±9.0	*F*=0.57, *P*=0.001	*t*=0.9, NS
DQOL–worry	19.4±8.6; 17.1±8.1	*F*=0.69, *P*=0.001	*t*=3.1, *P*=0.01
BDI–total	6.1±5.4; 7.7±6.8	*F*=0.67, *P*=0.001	*t*=2.8, *P*=0.01
DAS–diabetes conflict	19.8±11.2; 18.4±8.7	*F*=0.53, *P*=0.001	*t*=1.3, NS
Knowledge	NA; 43.2±4.2	—	—

Data are means±SD unless otherwise indicated. *F=0.77, P= 0.52, MANOVA; †no MANOVA performed because only one variable, BG risk index, was hypothesized to change; ‡F=2.4, P=0.1, MANOVA; §F=0.87, P=0.46, MANOVA; ‖F=5.6, P=0.005, MANOVA. DAS, Dyadic Adjustment Scale; DQOL, Daily Quality of Life; NA, not available.

Table G-64. Outcomes at Baseline, 6 and 12 month Followup

Variable	Baseline	6-month follow-up	12-month follow-up	Time *P* levels	Contrast 1* *P* levels	Contrast 2† *P* levels
Improved recognition of BG levels‡						
% Detection low BG	34±29	44±30	44±27	*F*=3.5; *P*=0.005	t=2.4; *P*=0.002	t=0.5; NS
% Detection high BG	51±24	55±26	53±27	*F*=3.1; *P* =0.001	t=1.7; *P*=0.05	t=0.9; NS
Accurate estimates	38±11	45±15	46±15	*F*=13.6; *P*=0.001	t=4.3; *P*=0.001	t=0.6; NS
Reduced extreme BG fluctuations§						
BG risk index	13.9±4.4	13.3±6.0	13.0±5.2	*F*=2.1; *P*=0.002	t=3.7; *P*= 0.001	t=0.01; NS
HbA1c	10.2±2.0	10.2±2.0	10.2±1.9	*F*=0.1; NS	t=0.0; NS	t=0.5; NS
Improved judgment‖						
% Decision to raise low BG	50±27	59±34	58±30	*F*=3.6; *P*= 0.005	t=2.6; *P*=0.01	t=2.2; *P*=0.5
% Decision to lower high BG	53±26	54±30	60±28	*F*=5.2; *P*=0.001	t=3.3; *P*=0.001	t=2.2; *P*=0.05
% Decision not to drive when low	48±33	50±36	51±31	*F*=2.0; *P*=0.01	t=2.7; *P*=0.005	T= 0.3; NS
Reduction of negative consequences¶						
DKA (total no.)	7	0	0	—	—	—
Severe hypoglycemia (mean episodes/month)	1.6±2.0	1.2±1.9	1.1±2.0	*F*=3.9; *P*=0.002	t - 2.3; *P*= 0.002	t = 0.8; NS
Motor vehicle violations (mean violations/month)	0.09±0.27	0.03±0.09	0.03±0.15	*F*=5.4; *P*=0.001	t=2.8; P=0.001	t = 0.4; NS
Improvement in psychological parameters#						
Hypoglycemia fear survey–worry	22±9.6	17.5±10.7	17.4±9.9	*F*=21.2; *P*=0.001	t=5.2; *P*=0.002	t = 0.8; NS
DQOL–impact	46.3±8.7	44.0±7.7	43.8±8.3	*F*=6.7; *P*=0.005	t=3.1; *P*=0.005	t = 1.0; NS
DQOL–worry	18.3±7.6	16.5±8.7	16.2±8.5	*F*=11.7; *P*=0.001	t=4.3; *P*=0.001	t = 0.8; NS
BDI–total	6.9±5.6	5.8±5.7	6.1±6.2	*F*=2.4; *P*=0.09	t=1.6; *P*=0.11	t = 0.6; NS
DAS–diabetes conflict	19.1±8.7	18.5±8.3	18.9± 8.7	*F*=0.5; NS	t=0.5; NS	t = 0.7; NS
Knowledge	43.2±4.2	46.8±3.3	46.3±3.5	*F*=61.7; *P*=0.001	T=8.2; *P*=0.001	t=1.4; NS

Data are means±SD unless otherwise indicated. *Contrast 1 compared the 6-month baseline with the 6-and 12-month follow-up data to determine whether there was a long-term benefit of BGAT-2; †contrast 2 compared posttreatment (assessment 3, Fig. 1); ‡*F* = 4.0, *P*=0.01, MANOVA; §no MANOVA was performed because only one variable, BG risk index, was hypothesized to change; ‖*F* = 2.7, *P*=0.05, MANOVA; ¶*F* = 4.5, *P*=0.005, MANOVA; #*F* 514.9, *P*=0.0001, MANOVA.

<table>
<tr><td colspan="15">Reference: Kinsley BT, Weinger K, Bajaj M, Levy CJ, Simonson DC, Quigley M, Cox DJ, Jacobson AM. Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in Type 1 diabetes. Diabetes Care 1999 Jul;22(7):1022-8.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td></tr>
<tr><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td><td colspan="3">✓</td></tr>
<tr><td>Research Question</td><td colspan="14">To determine the effect of BGAT on epinephrine and symptom responses to hypoglycemia in patients with T1DM enrolled in an intensive diabetes treatment (IDT) program.</td></tr>
<tr><td>Study Design</td><td colspan="14">RCT</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">1</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">T1DM</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Subjects were excluded if there was evidence of proliferative retinopathy or diabetic nephropathy, or a history of severe unrecognized hypoglycemia within the previous two years.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">T1DM. N=47 (23 males, 24 females). Mean age of 34±8 years. Duration of disease 3 – 15 years. Mean pre-study HbA_{1c} 9.0±1.2%.
See Table G-65</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Participants were followed over a four to five month period through an outpatient clinic with the goal of improving glycemic control as near to nondiabetic range as safely possible. They were seen monthly by study physicians, nurse educators, and a nutritionist. Participants had weekly telephone contact with a nurse educator to optimize glycemic control. During this period participants took three to five insulin injection per day and performed an average of five home BG measurements per day.
Participants were randomized to BGAT (treatment) or cholesterol education group.
Before and four months post-treatment participants underwent paired identical hypoglycemic insulin clamp (IDT) procedures.
At baseline and at each glucose level during the test, subjects completed the MSQ mood and symptom questionnaire.
HbA_{IC} was measured at baseline, before the beginning of IDT, at each monthly clinical visit, and at the final clinical visit.
BG meter data was downloaded to computer on the day of each IDT, providing BG data for 4 weeks before each of the studies.
Participants were asked to estimate their BG during each plateau phase of the IDT. BG estimation error was calculated as BG minus the estimated BG. BT estimation accuracy with the HHC by estimating and then measuring BG for 70 trials over a four week period preceding IDT initiation and again over a four week period immediately after treatment. Before each of the 70 trials participants recorded BG, relevant symptoms, and mood.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Data was reported as mean±SEM, except for demographic data.
Between-group differences in glycemic control, hypoglycemia frequency, low BG index, and counterregulatory hormones at specific glucose levels were tested with Student's t tests.
Within-group preintervention vs postintervention were tested with paired t tests.
Overall differences in counterregulatory hormone response to hypoglycemia were tested with ANOVA.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score=0.68</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Difference in frequency and extent of low blood glucose events
Difference in reduction in significant hypoglycemia
Difference in low blood glucose detection, symptoms, and appropriateness of treatment</td></tr>
<tr><td>Results</td><td colspan="14"><u>All included patients</u>: During the four months of IDT, glycemic control improved in both groups. Hypoglycemia frequency increased in both groups. No differences were noted in the severity of hypoglycemia.
Neurogenic and neuroglycopenic symptom scores during IDT increase with hypoglycemia but did not differ between groups before or four months after IDT. Self-reported neurogenic symptoms decreased in BGAT participants. Neuroglycopenic symptoms did not differ between groups.
BG estimation accuracy did not differ between groups before IDT. After IDT, BGAT participants had a greater improvement in detection of low BG and fewer undetected low BG readings. See Table G-66
<u>Subgroup of 26 individuals most at risk for hypoglycemia</u>: Subgroup identified during IDT. The following results pertain to this subgroup:
Comparing hypoglycemic episodes, there was an increase in the cholesterol education group, and no increase in the BGAT group.
Neurogenic and neuroglycopenic symptoms did not differ between groups.
BG estimation accuracy did not differ between groups before IDT. BGAT participants had fewer undetected low BG readings compared with the cholesterol education group. See Table G-68</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">BGAT may modify the severity of hypoglycemia associated with improved glycemic control in T1DM</td></tr>
</table>

Table G-65. Baseline Demographics

	Total group	At risk for hypoglycemia
n	47	26
Sex (M/F)	23 / 24	11 / 15
Age (years)	34±8 (19–50)	33±8 (19–50)
BMI (kg/m2)	25±3 (19–31)	24±3 (19–29)
Duration of type 1 diabetes (years)	9±3 (3–15)	9±3 (3–15)
Baseline HbA1 c(%)	9.0±1.2 (7.4–13.0)	8.9±1.4 (7.4–13.0)
Education (years)	16±2 (11–20)	16±2 (12–20)

Data are means±SD (range).

Table G-66. Counterregulatory Hormone Responses Before and After Treatment (All Included Patients)

	Control (*n*=22)		BGAT (*n*=25)	
	Baseline	Nadir	Baseline	Nadir
Norepinephrine (nmol/l)				
Before	1.08±0.08	1.78±0.19	1.14±0.07	1.74±0.17
After	1.24±0.10	2.04±0.19	1.28±0.10	2.41±0.22
ACTH (pmol/l)				
Before	3.0±0.5	15.2±3.2	3.3±0.5	18.2±3.6
After	5.4±1.7	18.6±3.3	5.2±1.0	18.3±2.9
Cortisol (nmol/l)				
Before	385±27	573±45	401±25	617±47
After	388±30	576±37	352±19	604±44
hGH (µg/l)				
Before	9±2	55±7	23 7	37±7
After	9±3	48±5	9±2	46±6

Data are means±SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

Table G-67. Symptom Scores (All Included Patients)

	Control (*n*=22)		BGAT (*n*=25)	
	Baseline	Nadir	Baseline	Nadir
Neurogenic				
Before	0.32±0.11	2.14±0.27	0.31±0.10	2.2±0.30
After	0.30±0.08	1.82±0.29	0.30±0.11	1.78±0.30
Neuroglycopenic				
Before	0.64±0.12	2.30±0.21	0.74±0.14	2.18±0.32
After	0.53±0.12	1.87±0.22	0.70±0.18	1.56±0.26

Data are means±SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

Table G-68. Counterregulatory Hormone Responses Before and After Treatment (26 High-Risk Patients)

	Control (*n*=12)		BGAT (*n*=14)	
	Baseline	**Nadir**	**Baseline**	**Nadir**
Norepinephrine (nmol/l)				
Before	1.12±0.10	1.94±0.30	1.16±0.11	1.60±0.16
After	1.30±0.12	2.00±0.15	1.08±0.08	2.05±0.20
ACTH (pmol/l)				
Before	3.7±0.7	16.7±5.1	3.5±0.8	13.4±3.2
After	7.6±2.9	16.8±5.4	5.1±1.5	12.2±1.6
Cortisol (nmol/l)				
Before	374±36	565±61	400±34	660±58
After	399±53	531±53	366±30	600±67
hGH (µg/l)				
Before	8±3	55±9	25±5	30±5
After	13±4	53±8	12±3	41±7

Data are means±SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

Table G-69. Symptom Scores (26 High-Risk Patients)

	Control (*n*=12)		BGAT (*n*=14)	
	Baseline	**Nadir**	**Baseline**	**Nadir**
Neurogenic				
Before	0.52±0.18	2.58±0.30	0.29±0.10	2.17±0.38
After	0.42±0.12	2.27±0.36	0.13±0.09	1.59±0.40
Neuroglycopenic				
Before	0.75±0.20	2.41±0.25	0.44±0.16	1.67±0.34
After	0.47±0.16	2.15±0.28	0.20±0.10	1.06±0.24

Data are means±SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

Reference: Cox DJ, Carter WR, Gonder-Frederick LA, Clarke WL, Pohl SL. Blood glucose discrimination training in insulin-dependent diabetes mellitus (IDDM) patients. Biofeedback Self Regul 1988 Sep;13(3):201-17.														
Key Questions Addressed	**1**		**2**		**3**		**4**							
							✓							
Research Question	To evaluate whether patients 'learn' to more accurately discriminate BG on the basis of internal cues (symptoms) or internal plus external (meals, time of day) BG cues.													
Study Design	Pre-Post													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	T1DM average of twice daily for periods ranging from 2 to 32 months												
	Exclusion Criteria	No chronic medications for neuropathy, cardiovascular problems, or 'other reasons'												
	Study population Characteristics	Used SMBG an average of twice daily for periods ranging from 2 to 32 months 6 male/10 female Age range: 22 to 67 years of age (mean=43.7 years of age) Duration of diabetes: 2 to 50 years (mean=10.3 years)												
	Generalizability to CMV drivers	Unclear												
Methods	Home Assessment: Participants completed intensive SMBG training program. Participants estimated BG t.i.d. (before routine daily SMBG) using both internal and external cues, over a 14 day period. Home assessment of BG estimation accuracy occurred twice, immediately following pre- and post- treatment evaluation. Half of the participants were assigned to enter their estimated and actual BG readings into hand held computer. The other half of the participants were assigned to enter their estimated and actual BG readings into provided homework sheets. All patients participated in a single treatment group utilizing the BGAT training program over the course of six weeks. For each class, participants read assignments, discussed content, and reviewed the previous week's homework. Part of the homework assignment consisted of recording internal and external BG cues, BG estimations, and actual BG measurements. Participants also plotted their estimated-actual BG on an Error Grid.													
Statistical Methods	Paired *t* test performed on pre/post AIs. Correlational analyses (post-hoc)													
Quality assessment	**Internal Validity**	**ECRI QCL I (see Appendix B)**												
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		N	N	NR	N	Y	Y	Y	NR	NR	Y	NR	Y	NR
	Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
		NR	NR	NR	NR	Y	Y	Y	Y	Y	Y	N	Y	
Relevant Outcomes Assessed	Difference in low blood glucose detection													
Results	There was a significant increase in BG estimation precision and sensitivity to hypoglycemia. There were significant correlations between pretreatment AI and improvement in pre/post AI. Less accurate participants demonstrated greater improvement.													
Authors' Comments	Improvement in estimation accuracy was related only to initial accuracy; those who were initially less accurate improved the most. Resulting estimations were still significantly less accurate than SMBG at the end of training.													

Table G-70. Actual and Estimated BG levels for Hospital and Home Assessments

		Time			
		Pre		Post	
Group	Assessment	Estimated *X/SD*	Actual *X/SD*	Estimated *X/SD*	Actual *X/SD*
Group control	Hospital	123/37	118/47	131/42	113/52
	Home	181/78	148/68	136/50	145/62
Treatment group	Hospital	133/40	128/55	129/46	117/55
	Home	153/62	173/81	148/64	165/74
Treatment group	Home	139/59	132/62	132/58	143/67

Table G-71. Mean Improvement

	Study I		Study II
Group	Hospital	Hòme	Home
Control group	+4.6/40%	−0.4/40%	
Experimental group	+15.4/70%	+13.8/70%[a]	+17.9/87%[a]

[a]Significant chi squares.

<table>
<tr><td colspan="14">Reference: Cox DJ, Gonder-Frederick LA, Julian D, Cryer P, Herrman-Lee J, Richards FE, Clarke W. Intensive Versus Standard Blood Glucose Awareness Training (BGAT) with Insulin-Dependent Diabetes: Mechanisms and Ancillary Effects. Psychosomatic Medicine 1991 53:453-462.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="7">4</td></tr>
<tr><td></td><td colspan="3"></td><td colspan="3"></td><td colspan="7">✓</td></tr>
<tr><td>Research Question</td><td colspan="13">What is the relative efficacy of an Intensive BGAT to enhance patient accuracy of BG estimation and metabolic control compared to standard BGAT and control?
What are the mechanisms and ancillary effects of BGAT?</td></tr>
<tr><td>Study Design</td><td colspan="13">RCT</td></tr>
<tr><td>USPSTF Level</td><td colspan="13">I</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="12">IDDM for at least 2 years. Insulin usage since diagnosis. Using SMBG.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="12">No history of the following: cardiac disease, hypertension, seizure activity, severe psychiatric disturbance. No chronic medications other than insulin.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="12">N=39
See Table G-72 for complete descriptive data.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Methods</td><td colspan="13">Potential subjects solicited by newspaper advertisement. Incentive included: $200.00 at pre-treatment conclusion evaluation, $100.00 at post-treatment conclusion evaluation; three free glycosylated hemoglobin tests; thorough diabetic evaluation; free SMBG supplies during Accuracy and Treatment phases. Potential subjects completed a screening questionnaire to solicit information on diabetic history, medication usage, psychiatric history, and demographic information.
Qualified subjects participated in a group orientation meeting where initial glycosylated hemoglobin was drawn.
SMBG Frequency-I: Subjects were given a Glucometer-M (Ames Co., Elkhart, IN) memory reflectance meter to use for 2 weeks, just as they usually used their own meter. This gave SMBG frequency readings for 14 consecutive days.
Accuracy-I: Subjects were then given a beeper which randomly activated four times a day for 10 days. At the time of the beep, subjects recorded the time, estimated BG value, and then performed SMBG.
Assessment-I: Individual subjects went to the study laboratory and completed a series of questionnaires, including the Diabetes Knowledge Questionnaire and the Hypoglycemic Fear Survey.
Hospitalization: Subjects were admitted overnight to the clinical research unit for intravenous insulin to determine ability to counter-regulate. On the second day, subjects BG was lowered and elevated over a five hour period. On both days, the subjects completed a symptom checklist and estimated BG levels every 10 to 30 minutes while concurrent BG determinations were made.
Treatment: 7 weeks
Standard BGAT (7 weekly sessions, BGAT manual readings and homework, including daily systematic recording of internal and external cues and estimated and actual BG levels).
Intensive BGAT began during hospitalization, where 1. subjects were provided with immediate BG feedback while both hypo-and hyperglycemic. At these times, subjects a) described the gestalt* of their experience on audio tape, b) rated perceived symptoms on a standard checklist, c) estimated BG level, d) were given feedback on actual BG levels, e) if estimated-actual BG was discrepant, were asked to scan for missed or erroneously interpreted signals. Subjects also 2. analyzed the symptoms checklist ratings for consistent relationships between hypo- and hyperglycemia. Feedback about the subjects idiosyncratic symptom-BG relationship was provided during the second BGAT class. During class three, subjects 3. listened to and were given a copy of the audiotape of the self-descriptive experiences of hypo- and hyperglycemia. This allowed Intensive BGAT subjects to recall how they felt and identify signs of neuroglycopenia.
Control/Placebo: Subjects attended group meetings and kept diaries. Classes led by local experts addressed diabetes-related subjects such as pregnancy and pancreatic transplantation. Diaries involved recordings of daily stress factors and diabetic self-care behaviors such as insulin usage, calories consumed, exercise performed, and SMBG results.
Accuracy II: Post treatment, subjects repeated Accuracy I protocol.
SMBG Frequency II: Post Accuracy II, subjects repeated SMBG Frequency I protocol.
Assessment II: Eight weeks after last class subjects repeated all questionnaires and had third glycosylated hemoglobin blood draw.</td></tr>
<tr><td>Statistical Methods</td><td colspan="13">BG estimation was evaluated using the Error Grid Analysis, with separate t tests to determine significant pre-post shifts in specific Error Grid zones.
Repeated measures ANOVA (pre-post x treatment group)</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score=7.5</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="13">Difference in frequency and extent of high and low blood glucose events
Difference in reduction in significant hypoglycemia
Difference in low blood glucose detection and symptoms</td></tr>
</table>

Results	Both BGAT and Intensive BGAT groups increased accurate estimates and sensitivity to hyperglycemia. Undetected hyperglycemia was lower for BGAT subjects. BGAT resulted in a nonsignificant reduction of percent undetected hypoglycemia BG's. Only the Intensive BGAT group demonstrated significant pre- post- reductions in glycosylated hemoglobin compared with the control group. See Table G-73
Authors' Comments	Intensive BGAT did not differ significantly from BGAT in improving estimation accuracy. Relative to BGAT, Intensive BGAT demonstrated trends toward: better post-treatment accuracy; greater mean improvement in detection of hypoglycemia and hyperglycemia; significant improvement in metabolic control for those who had poor control initially. BGAT did not reduce uncertainty of BG status or fear of hypoglycemia.

* encouraged to become aware of their own feelings, behaviors, and effect upon their environment.

Table G-72. Baseline Demographic Data for Three Study Groups

	N	Age	Dur	m/f	HgbA1	Insul	CR/NCR
Control	14	33.8	11.2	5/8	11.4	0.62	6/3
Standard BGAT	13	33.7	13.0	5/8	10.4	0.65	6/0
Intensive BGAT	12	31.1	12.7	4/8	12.8	0.67	7/2

[a] Dur, Mean duration of disease; m/f, number of male/female subjects; HgbA1, mean glycosylated hemoglobin at orientation, see Figure 5; Insul, average daily insulin dosage in units/kg; CR/NCR, number of subjects who clearly either counter-regulated or did not counter-regulate during insulin infusion hypoglycemia. Some subjects were not categorized because of equivocal findings.

Table G-73. Undetected Hypoglycemic SMBG Readings in Study Groups

	Hyperglycemia					Hypoglycemia				
	No. SMBG >180 mg/dl		% Undetected Lower D + E zones		Pre-Post % Reduction of ↓D + E errors	No. SMBG <70 mg/dl		% Undetected Upper D + E zones		Pre-Post % Improvement
	Pre	Post	Pre	Post[a]		Pre	Post	Pre	Post	
Intensive BGAT	202	180	13%	3%	−77%	47	53	51%	24%	−51%
Standard BGAT	213	188	19%	8%	−58%	43	56	46%	36%	−23%
Control	307	293	12%	16%	+33%	39	43	62%	61%	−2%

[a] ANOVA $p < 0.01$.

<table>
<tr><td colspan="15">Reference: Reference: Cox DJ, Gonder-Frederick LA, Herrman-Lee JH, Julian DM, Carter,WR, Clarke WL. Effects and Correlates of Blood Glucose Awareness Training (BGAT) among Patients with IDDM. Diabetes Care 12:313-8 (1989).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="7">4</td></tr>
<tr><td></td><td colspan="3"></td><td colspan="3"></td><td colspan="7">✓</td></tr>
<tr><td>Research Question</td><td colspan="14">Would IDDM patients learn to improve accuracy of BG estimations and have improved metabolic control.</td></tr>
<tr><td>Study Design</td><td colspan="14">RCT</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">I</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">IDDM of 2 years duration
Insulin use since IDDM diagnosis</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">No diabetic complications
No use of hypertension or tricyclic medications.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">N=22 (8 males, 14 females)
Mean age: 32.4 years old (SD ± 8.5 years)
Mean duration of IDDM: 10.6 years (SD ± 7.7 years)
Average SMBG experience 8 to 48 mo (mean 27.4)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Potential subjects recruited from newspaper advertisements.
Subjects provided with free medical evaluations and $300 in exchange for completion of diabetes research study participation.
15 subjects randomized to BGAT group and seven subjects randomized to control group.
To evaluate the effects of BGAT on metabolic control, HbA_{IC} measured at initial recruitment session, two months later at pretreatment hospitalization, and at two months posttreatment.
To evaluate the effects of SMBG frequency on accuracy of BG estimation, subjects were given a memory meter (Ames, Elkhart, IN) for 2 weeks after recruitment. Subjects measured BG at their routine frequency.
To evaluate accuracy of BG estimation, subjects were given a beeper which activated at 4 random times a day for 10 days. Each time activation occurred subjects estimated BG and then collected and recorded SMBG. This was repeated pre- and post-treatment.
To evaluate ability to counterregulate to hypoglycemia, subjects were admitted to the research unit for testing. The night before testing, subjects received overnight IV regular insulin to maintain euglycemia. In the morning subjects received a two hr. continuous infusion of insulin and BG concentrations were continuously monitored. Subjects were monitored is signs of neuroglycopenia occurred. Failure to counterregulate was noted.
The BGAT group met for seven consecutive weekly classes to focus on BGAT manual readings and homework review. At the end of each week BGAT subjects identified sources of information which led to accurate BG estimations.
The Control group participated in group meetings where they discussed the role of psychological stress on metabolic control, and recorded SMBG, insulin, food eaten, and stress levels in daily diaries.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">BG estimation was evaluated using the Error Grid Analysis
Repeated measures ANOVA
t tests</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality=7.2</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Difference in frequency and extent of high and low blood glucose events.
Difference in reduction in significant hypoglycemia.
Difference in low blood glucose detection and symptoms.</td></tr>
<tr><td>Results</td><td colspan="14">BGAT group demonstrated significant improvement in accuracy of blood glucose estimate. In addition, the BGAT group demonstrated greater sensitivity to hyperglycemia and fewer benign errors, and a significant reduction in HbA_1. No such improvement in accuracy was observed in the control group.
No relationship between posttreatment HbA_1 and accuracy was observed, which indicates that greater improved accuracy did not directly lead to better metabolic control or vise versa (See Table G-74).</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">BGAT group participants improved BG estimation accuracy and glycosylated hemoglobin.
Post-treatment improvement was associated with pretreatment BG estimation accuracy and the ability to counterregulate to insulin induced hypoglycemia.</td></tr>
</table>

Table G-74. Correlation Matrix Between Pretreatment Measures and Improvement in Accuracy after BGAT

	Preaccuracy Index	Post BGAT δ – accuracy Index
Preaccuracy Index		-.43†
SMBG frequency in 2 week	-.20	-.33
Months of SMBG experience	.34†	-.13
Ability to counterregulate	-.18	.61§
HbA_1*	.30	-.03

SMBG: self monitoring blood glucose

*Hospital HbA_1 was correlated with the preaccuracy index, whereas posttreatment HbA_1 was correlated with the δ – accuracy index.

†P=0.06; ‡ P=0.08; § P=0.013; all other values not significant

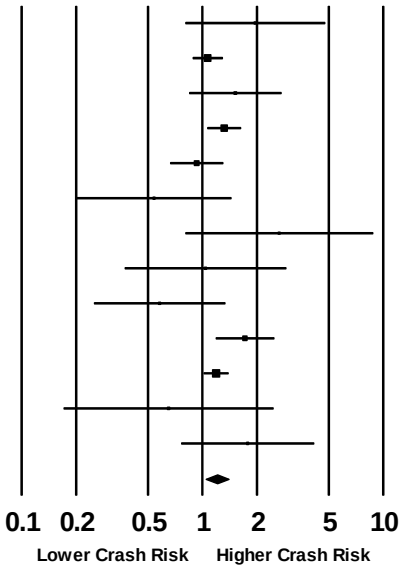
Reference: Reference: Cox DJ, Gonder-Frederick LA, Polonsky W, Schlundt D, Julian DM, Clarke WL. A Multicenter Evaluation of Blood Glucose Awareness Training-II. Diabetes Care April 1995 (18) 4:523-28.														
Key Questions Addressed	1		2		3		4							
							✓							
Research Question	To assess whether BGAT-II would result in increasing sensitivity to low BG events													
Study Design	Pre-Post study													
USPSTF Level	II-3													
Population	**Inclusion Criteria**	IDDM of 2 years duration Insulin use since IDDM diagnosis Routine measure of BG with a meter ≥ b.i.d.												
	Exclusion Criteria	No clinical history of depression or substance abuse.												
	Study population Characteristics	N=78 (28 males, 50 females) Mean age: 38.2 years old (SD ± 9 years) Mean duration of IDDM: 19.3 years (SD ± 10.4 years)												
	Generalizability to CMV drivers	Unclear												
Methods	Potential subjects recruited from newspaper advertisements, notices posted in diabetes clinics, and direct physician referral. Subjects received as assessment including an HbA1c, assay and use of a hand help computer to be used for 50 trials over a 3-4 week period just before routine SMBG, whenever they felt BG fluctuations and when they anticipated their BG to be either high or low. For each trial, subjects first entered an estimated current BG, rated 12 symptoms, performed SMBG, and entered this reading. The BGAT-II classes met for consecutive weekly classes to focus on BGAT-II manual readings and homework review. Subjects then put the information obtained from readings, classes, and homework into practice. Data obtained during practice was recorded by the subject. One week after the last BGAT-II class, subjects performed BG readings as with pre-treatment. One month after the end of BGAT-II training, subjects returned the hand-held computers.													
Statistical Methods	BG estimation was evaluated using the Error Grid Analysis Repeated measures ANOVA *t* tests													
Quality assessment	Internal Validity	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y		
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Difference in frequency and extent of high and low blood glucose events. Difference in reduction in significant hypoglycemia. Difference in low blood glucose detection and symptoms.													
Results	BGAT participants demonstrated improvement in accuracy of blood glucose estimate. Reduced-awareness subjects experienced a significant improvement in detection of low BG.													
Authors' Comments	BGAT-II was effective in improving overall accuracy of BG estimation.													

Appendix H: Sensitivity Analyses

Sensitivity Analyses (Key Question 1)

Figure H-1. Random Effects Meta-Analysis

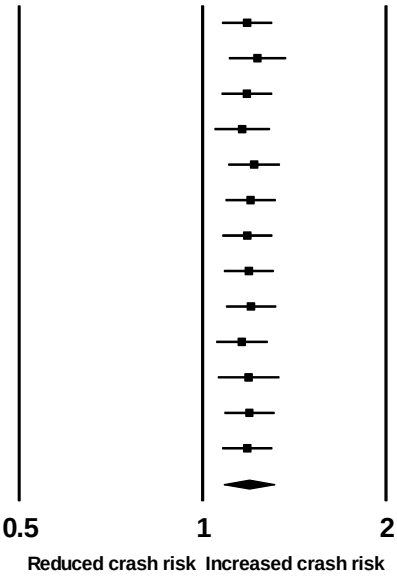
Study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Cox	1.960	0.800	4.802	1.472	0.141
Laberge-Nadeau	1.070	0.880	1.301	0.678	0.498
De Klerk	1.520	0.840	2.750	1.384	0.166
Hansotia	1.320	1.060	1.644	2.481	0.013
Stevens	0.930	0.660	1.310	-0.415	0.678
Eadington	0.540	0.200	1.458	-1.216	0.224
Songer	2.660	0.800	8.845	1.596	0.111
Davis	1.040	0.370	2.923	0.074	0.941
Ysander (1970)	0.580	0.250	1.346	-1.269	0.205
Campbell	1.720	1.180	2.507	2.821	0.005
Crancer	1.190	1.010	1.402	2.079	0.038
Ysander (1966)	0.650	0.170	2.485	-0.630	0.529
Waller	1.780	0.760	4.169	1.328	0.184
	1.200	1.037	1.390	2.440	0.015



Results of random effects model meta-analysis show that findings of original analysis are robust

Figure H-2 Risk Ratio (One Study Removed at a Time)

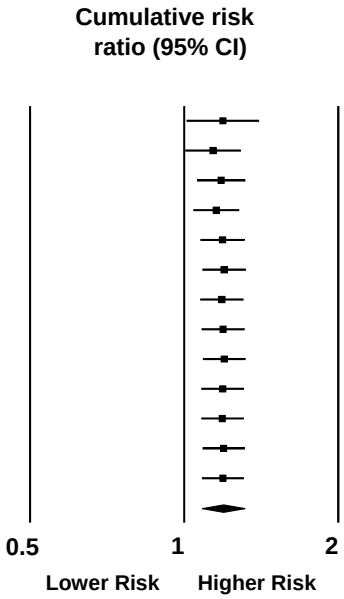
Study	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Cox	1.183	1.075	1.303	3.439	0.001
Laberge-Nadeau	1.231	1.103	1.373	3.718	0.000
De Klerk	1.183	1.074	1.303	3.398	0.001
Hansotia	1.162	1.045	1.292	2.773	0.006
Stevens	1.215	1.100	1.342	3.844	0.000
Eadington	1.199	1.089	1.320	3.710	0.000
Songer	1.184	1.076	1.303	3.460	0.001
Davis	1.192	1.083	1.312	3.585	0.000
Ysander (1970)	1.201	1.091	1.323	3.744	0.000
Campbell	1.161	1.052	1.281	2.958	0.003
Crancer	1.190	1.059	1.339	2.910	0.004
Ysander (1966)	1.194	1.085	1.314	3.630	0.000
Waller	1.184	1.076	1.304	3.449	0.001
	1.190	1.082	1.309	3.576	0.000

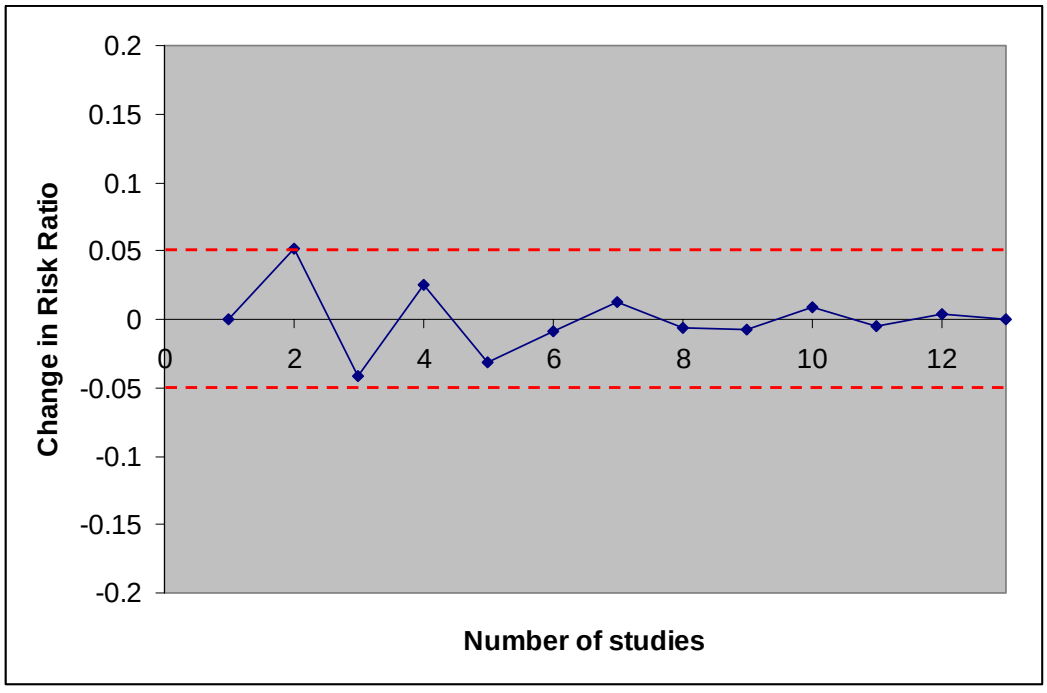


Results of analysis where one study removed at a time show that findings of original analysis are robust.

Figure H-3. Fixed Effects Cumulative Meta-Analysis (Ordered by Weight)

Study	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Crancer	1.190	1.010	1.402	2.079	0.038
Lab-Nadeau	1.139	1.004	1.291	2.029	0.042
Hansotia	1.181	1.059	1.317	2.993	0.003
Stevens	1.156	1.041	1.282	2.727	0.006
Campbell	1.188	1.075	1.314	3.379	0.001
De Klerk	1.197	1.084	1.321	3.562	0.000
Ysander ('70)	1.185	1.074	1.307	3.390	0.001
Waller	1.191	1.081	1.313	3.519	0.000
Cox	1.198	1.088	1.320	3.658	0.000
Eadington	1.189	1.080	1.310	3.523	0.000
Davis	1.188	1.079	1.308	3.514	0.000
Songer	1.194	1.085	1.314	3.630	0.000
Ysander ('66)	1.190	1.082	1.309	3.576	0.000
	1.190	1.082	1.309	3.576	0.000

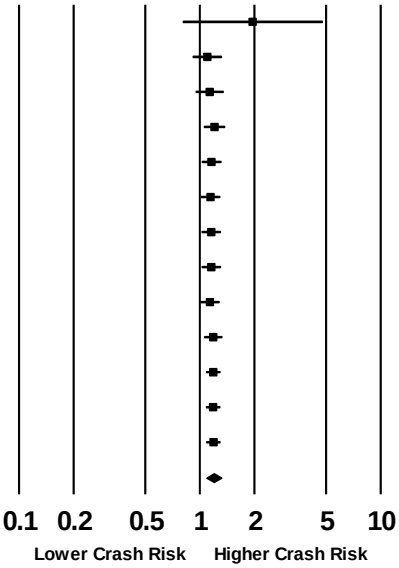


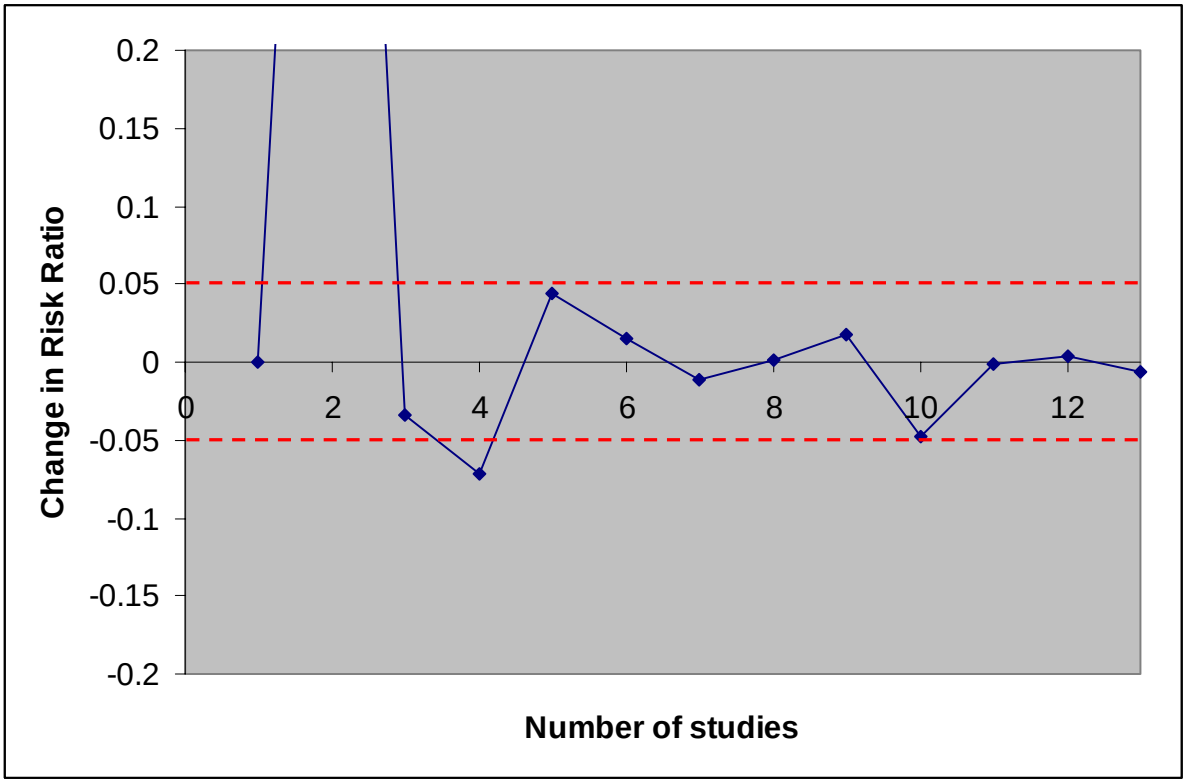


Results of cumulative meta-analysis show that results of original analysis are robust.

Figure H-4. Fixed-Effect Cumulative Meta-Analysis (Ordered by Pub. Date: Most Recent First)

Study	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Cox	1.960	0.800	4.802	1.472	0.141
Laberge-Nadeau	1.100	0.909	1.331	0.976	0.329
De Klerk	1.134	0.945	1.360	1.354	0.176
Hansotia	1.206	1.049	1.387	2.625	0.009
Stevens	1.162	1.021	1.323	2.274	0.023
Eadington	1.147	1.009	1.305	2.097	0.036
Songer	1.158	1.019	1.316	2.255	0.024
Davis	1.157	1.019	1.313	2.247	0.025
Ysander (1970)	1.139	1.005	1.291	2.033	0.042
Campbell	1.187	1.054	1.337	2.820	0.005
Crancer	1.188	1.079	1.308	3.503	0.000
Ysander (1966)	1.184	1.076	1.304	3.449	0.001
Waller	1.190	1.082	1.309	3.576	0.000
	1.190	1.082	1.309	3.576	0.000

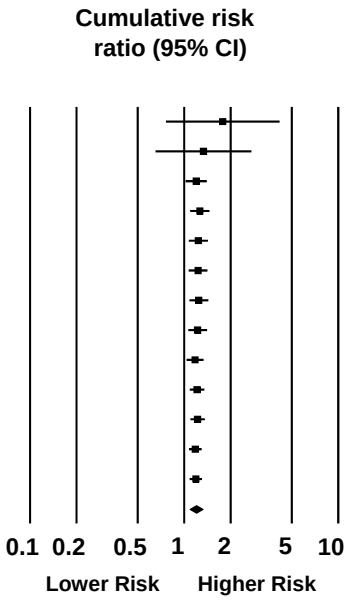




Results of cumulative meta-analysis show that results of original analysis are robust.

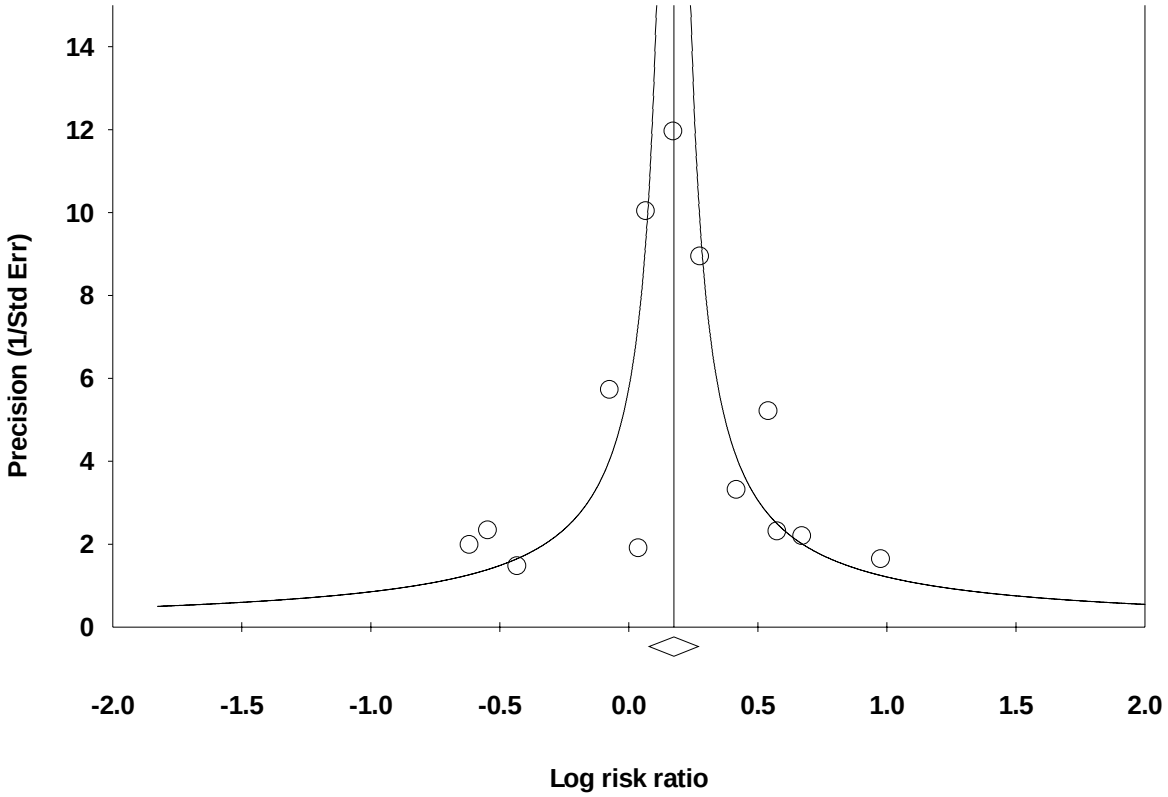
Figure H-5. Fixed-Effect Cumulative Meta-Analysis (Ordered by Pub. Date: Most Recent Last)

Study	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Waller	1.780	0.760	4.169	1.328	0.184
Ysander (‘66)	1.333	0.650	2.735	0.784	0.433
Crancer	1.197	1.020	1.404	2.201	0.028
Campbell	1.265	1.092	1.465	3.128	0.002
Ysander (‘70)	1.236	1.069	1.429	2.863	0.004
Davis	1.232	1.067	1.422	2.845	0.004
Songer	1.245	1.080	1.436	3.015	0.003
Eadington	1.224	1.063	1.410	2.811	0.005
Stevens	1.177	1.033	1.341	2.442	0.015
Hansotia	1.212	1.084	1.356	3.367	0.001
De Klerk	1.222	1.094	1.364	3.565	0.000
Lab-Nadeau	1.183	1.075	1.303	3.439	0.001
Cox	1.190	1.082	1.309	3.576	0.000
	1.190	1.082	1.309	3.576	0.000



Results of cumulative meta-analysis show that results of original analysis are robust.

Figure H-6. Publication Bias Test: Funnel Plot of Precision vs. LnRR



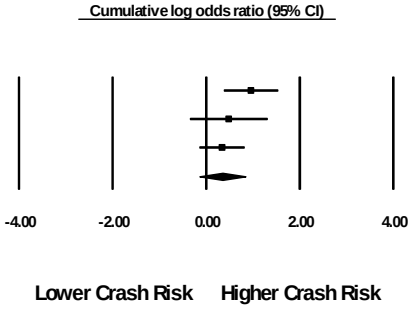
Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		1.19026	1.08190	1.30948	1.20015	1.03656	1.38955	18.15615
Adjusted values	0	1.19026	1.08190	1.30948	1.20015	1.03656	1.38955	18.15615

Analysis finds no evidence of publication bias

Figure H-7. Odds Ratio Analysis 1 (All)-Sensitivity Analysis 1: Cumulative REMA

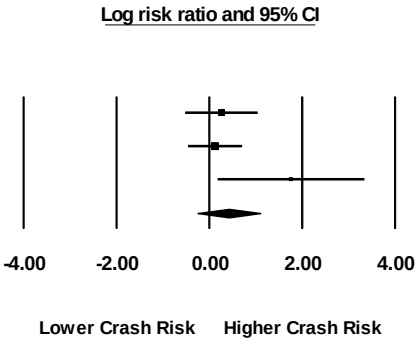
Study name	Subgroup within study	Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Koepsell (all)	Overall	0.960	0.300	0.090	0.372	1.548	3.200	0.001
Gressert (all)	Overall	0.483	0.427	0.183	-0.354	1.321	1.131	0.258
McGwin (all)	Overall	0.339	0.250	0.063	-0.152	0.830	1.354	0.176
		0.339	0.250	0.063	-0.152	0.830	1.354	0.176



Findings of cumulative REMA show that original REMA is not Robust.

Figure H-8. Odds Ratio Analysis 2 (Insulin Users)-Sensitivity Analysis 1: REMA

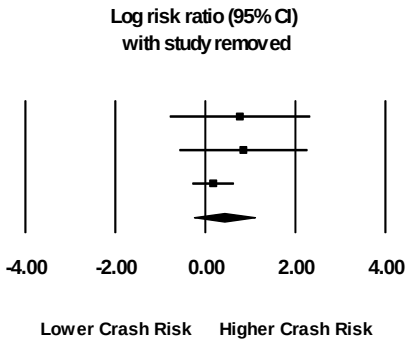
Study name	Statistics for each study						
	Log risk ratio	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McGwin	0.262	0.402	0.162	-0.525	1.050	0.653	0.514
Gressert	0.122	0.300	0.090	-0.465	0.710	0.408	0.683
Koepsell	1.758	0.810	0.656	0.171	3.345	2.171	0.030
	0.414	0.345	0.119	-0.263	1.091	1.199	0.231



Findings of primary FEMA are stable.

Figure H-9 Odds Ratio Analysis 2 (Insulin Users)-Sensitivity Analysis 2: One Study Removed at a Time

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McGwin	0.767	0.799	0.639	-0.800	2.334	0.960	0.337
Gressert	0.845	0.729	0.532	-0.584	2.274	1.159	0.247
Koepsell	0.172	0.240	0.058	-0.299	0.643	0.717	0.473
	0.414	0.345	0.119	-0.263	1.091	1.199	0.231



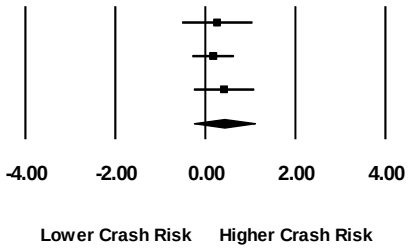
Findings of primary FEMA not stable.

Figure H-10. Odds Ratio Analysis 2 (Insulin Users)-Sensitivity Analysis 3: Cumulative FEMA

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McGwin	0.262	0.402	0.162	-0.525	1.050	0.653	0.514
Gressert	0.172	0.240	0.058	-0.299	0.643	0.717	0.473
Koepsell	0.414	0.345	0.119	-0.263	1.091	1.199	0.231
	0.414	0.345	0.119	-0.263	1.091	1.199	0.231

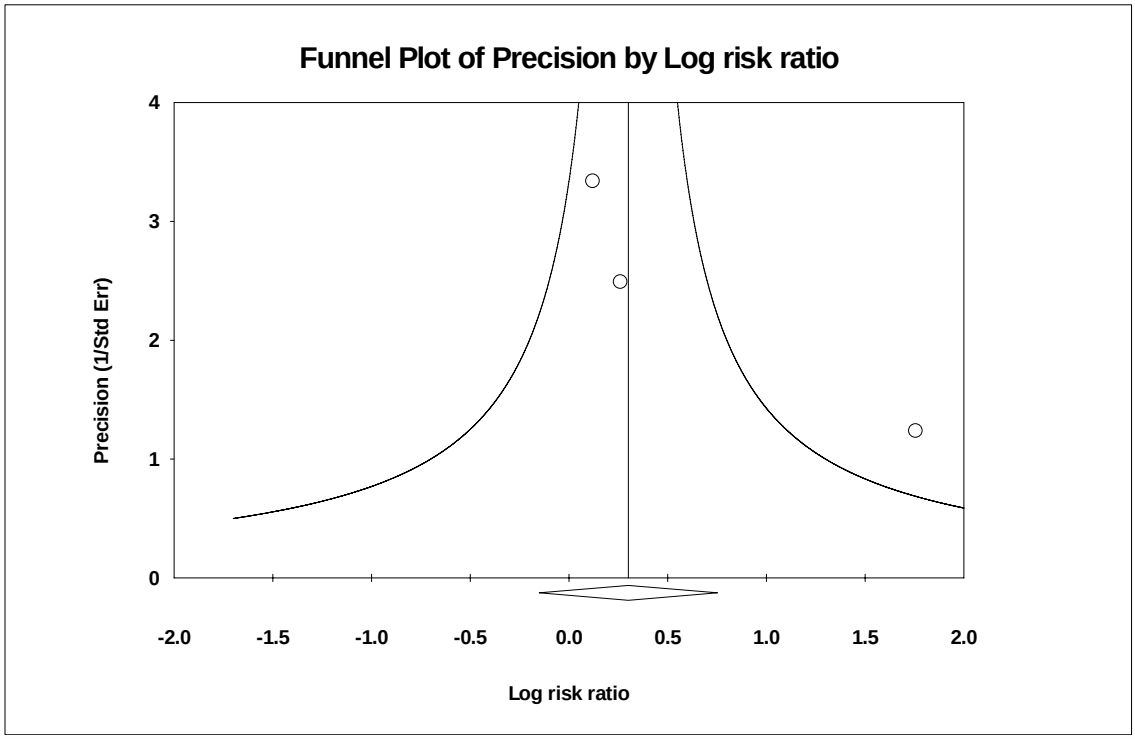
Cumulative statistics

Cumulative log risk ratio (95% CI)



Findings of primary FEMA not stable.

Figure H-11. Odds Ratio Analysis 2 (Insulin Users)-Sensitivity Analysis 4: Publication Bias Test



Duval and Tweedie's trim and fill

	Studies Trimmed	Fixed Effects Point Estimate	Fixed Effects Lower Limit	Fixed Effects Upper Limit	Random Effects Point Estimate	Random Effects Lower Limit	Random Effects Upper Limit	Q Value
Observed values		0.30059	-0.15091	0.75209	0.41408	-0.26280	1.09095	3.60106
Adjusted values	0	0.30059	-0.15091	0.75209	0.41408	-0.26280	1.09095	3.60106

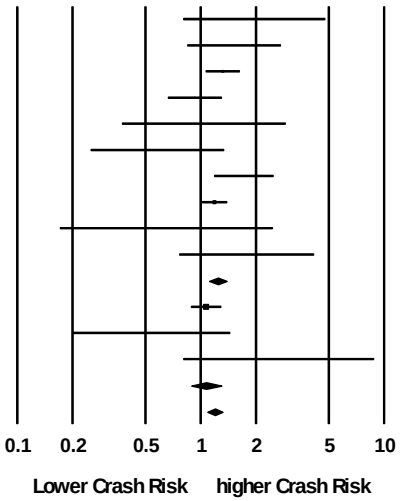
Analysis finds no evidence of publication bias

Appendix I. Exploratory Analyses

Exploratory Analyses for Key Question 1

Figure I-1. Effect of Exposure on LnRR

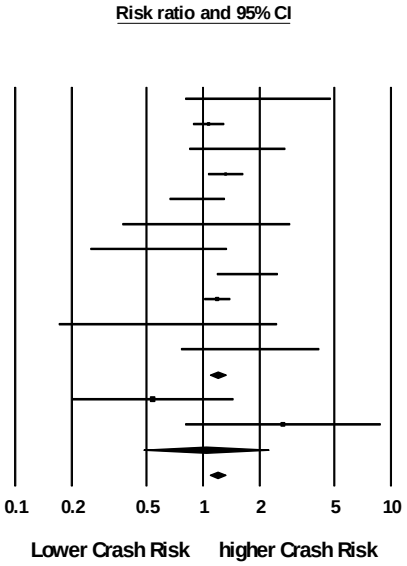
Group by Exposure status	Study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
0.00	Cox	1.960	0.800	4.802	1.472	0.141
0.00	De Klerk	1.520	0.840	2.750	1.384	0.166
0.00	Hansotia	1.320	1.060	1.644	2.481	0.013
0.00	Stevens	0.930	0.660	1.310	-0.415	0.678
0.00	Davis	1.040	0.370	2.923	0.074	0.941
0.00	Ysander (1970)	0.580	0.250	1.346	-1.269	0.205
0.00	Campbell	1.720	1.180	2.507	2.821	0.005
0.00	Crancer	1.190	1.010	1.402	2.079	0.038
0.00	Ysander (1966)	0.650	0.170	2.485	-0.630	0.529
0.00	Waller	1.780	0.760	4.169	1.328	0.184
0.00		1.235	1.106	1.379	3.746	0.000
1.00	Laberge-Nadeau	1.070	0.880	1.301	0.678	0.498
1.00	Eadington	0.540	0.200	1.458	-1.216	0.224
1.00	Songer	2.660	0.800	8.845	1.596	0.111
1.00		1.068	0.883	1.290	0.677	0.498
Overall		1.190	1.082	1.309	3.576	0.000



No evidence of a difference in findings of studies that controlled for exposure and those that did not.

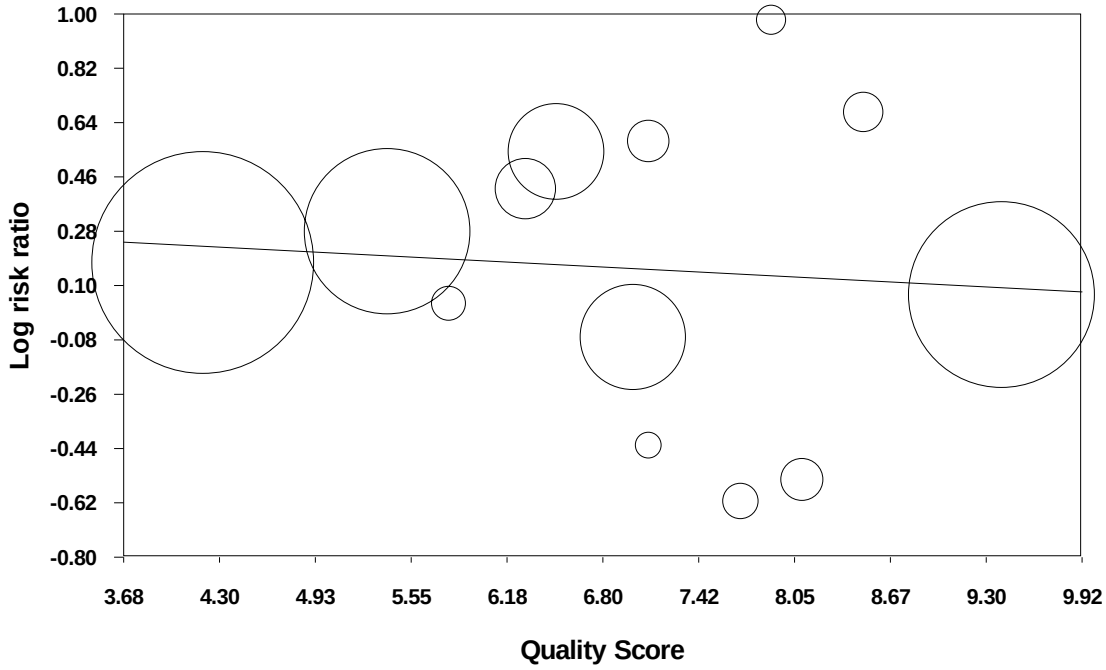
Figure I-2 Effect of Treatment on LnRR

Model	Group by All Type I	Study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	0.00	Cox	1.960	0.800	4.802	1.472	0.141
	0.00	Laberge-Nadeau	1.070	0.880	1.301	0.678	0.498
	0.00	De Klerk	1.520	0.840	2.750	1.384	0.166
	0.00	Hansotia	1.320	1.060	1.644	2.481	0.013
	0.00	Stevens	0.930	0.660	1.310	-0.415	0.678
	0.00	Davis	1.040	0.370	2.923	0.074	0.941
	0.00	Ysander (1970)	0.580	0.250	1.346	-1.269	0.205
	0.00	Campbell	1.720	1.180	2.507	2.821	0.005
	0.00	Crancer	1.190	1.010	1.402	2.079	0.038
	0.00	Ysander (1966)	0.650	0.170	2.485	-0.630	0.529
	0.00	Waller	1.780	0.760	4.169	1.328	0.184
Fixed	0.00		1.193	1.084	1.313	3.594	0.000
	1.00	Eadington	0.540	0.200	1.458	-1.216	0.224
	1.00	Songer	2.660	0.800	8.845	1.596	0.111
Fixed	1.00		1.032	0.480	2.218	0.080	0.936
Fixed	Overall		1.190	1.082	1.309	3.576	0.000



REMA for insulin subgroup found no increased crash risk. Analysis very low power. No difference in crash risk between groups.

Figure I-3. L'Abbe Plot Showing Relationship between Study Quality Score and Log Risk Ratio



Mixed effects regression (unrestricted maximum likelihood)

	Point estimate	Standard error	Lower limit	Upper limit	Z-value	p-Value
Slope	-0.02643	0.02398	-0.07344	0.02058	-1.10194	0.27049
Intercept	0.34082	0.15888	0.02942	0.65221	2.14515	0.03194
Tau-squared	0.00000					

	Q	df	p-value
Model	1.21426	1.00000	0.27049
Residual	16.94189	11.00000	0.10961
Total	18.15615	12.00000	0.11103

Slope not significantly different from zero. No evidence of a relationship between quality score and log risk ratio

Figure I-4. Subgroup analysis: Crash Risk in Moderate vs. Low Quality Studies

Group by High quality?	Study	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
0.00	De Klerk	1.520	0.840	2.750	1.384	0.166
0.00	Hansotia	1.320	1.060	1.644	2.481	0.013
0.00	Stevens	0.930	0.660	1.310	-0.415	0.678
0.00	Eadington	0.540	0.200	1.458	-1.216	0.224
0.00	Songer	2.660	0.800	8.845	1.596	0.111
0.00	Davis	1.040	0.370	2.923	0.074	0.941
0.00	Campbell	1.720	1.180	2.507	2.821	0.005
0.00	Crancer	1.190	1.010	1.402	2.079	0.038
0.00	Ysander (1966)	0.650	0.170	2.485	-0.630	0.529
0.00	Waller	1.780	0.760	4.169	1.328	0.184
0.00		1.238	1.108	1.384	3.764	0.000
1.00	Cox	1.960	0.800	4.802	1.472	0.141
1.00	Laberge-Nadeau	1.070	0.880	1.301	0.678	0.498
1.00	Ysander (1970)	0.580	0.250	1.346	-1.269	0.205
1.00		1.066	0.885	1.284	0.671	0.502

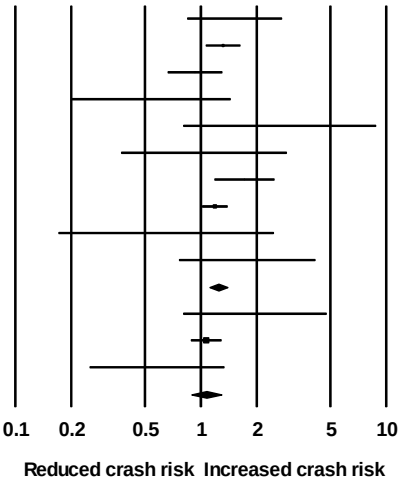
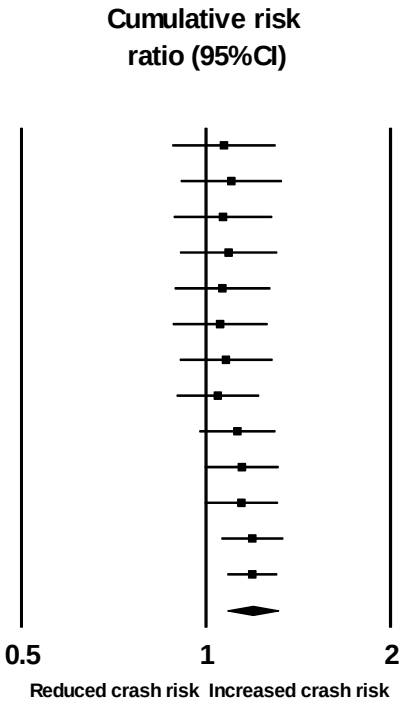


Figure I-5. Fixed-Effects Cumulative Meta-Analysis: Studies Added in Order of Decreasing Study Quality

Study	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Laberge-Nadeau	1.070	0.880	1.301	0.678	0.498
Cox	1.100	0.909	1.331	0.976	0.329
Ysander (1970)	1.066	0.885	1.284	0.671	0.502
Songer	1.089	0.906	1.309	0.908	0.364
Eadington	1.064	0.888	1.275	0.671	0.502
Ysander (1966)	1.055	0.881	1.262	0.581	0.561
Waller	1.078	0.905	1.285	0.842	0.400
Stevens	1.046	0.894	1.223	0.561	0.575
Campbell	1.125	0.974	1.300	1.599	0.110
De Klerk	1.144	0.994	1.316	1.880	0.060
Davis	1.142	0.994	1.312	1.873	0.061
Hansotia	1.190	1.059	1.339	2.910	0.004
Crancer	1.190	1.082	1.309	3.576	0.000
	1.190	1.082	1.309	3.576	0.000



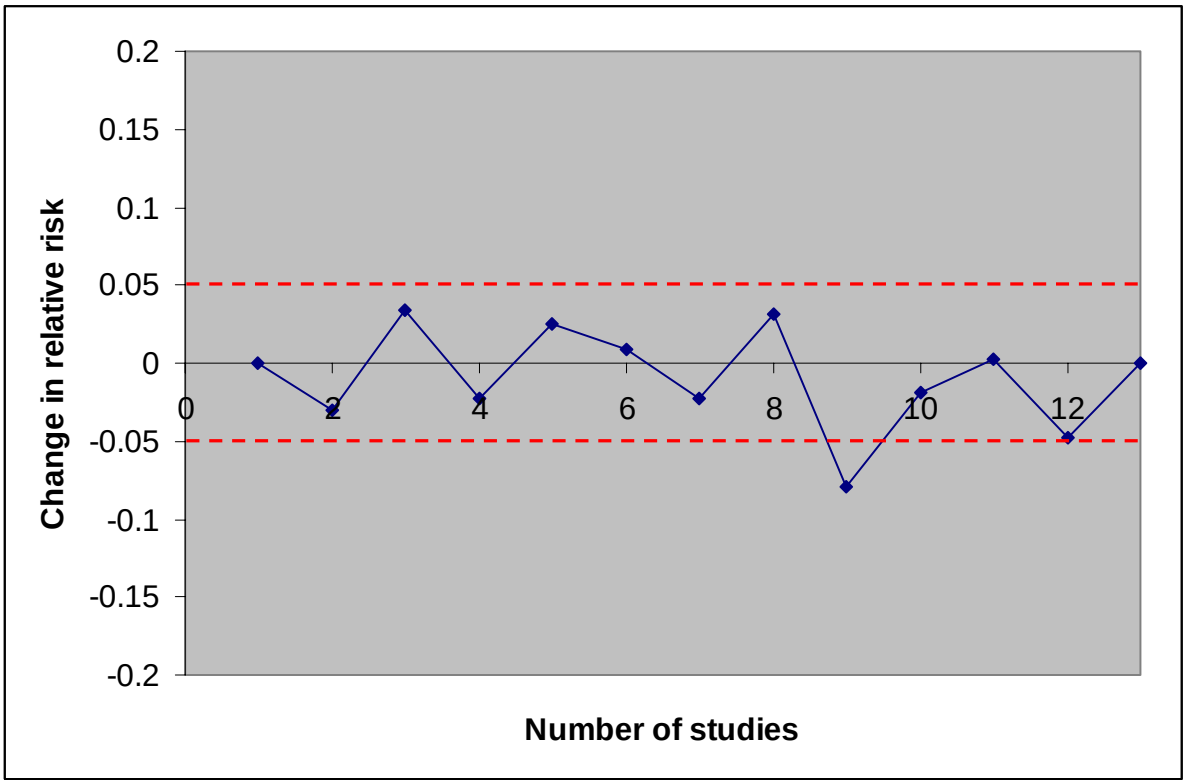
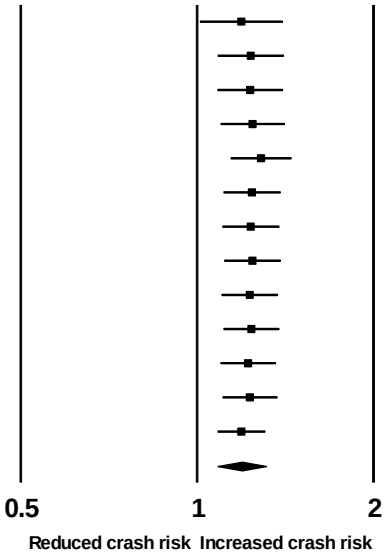
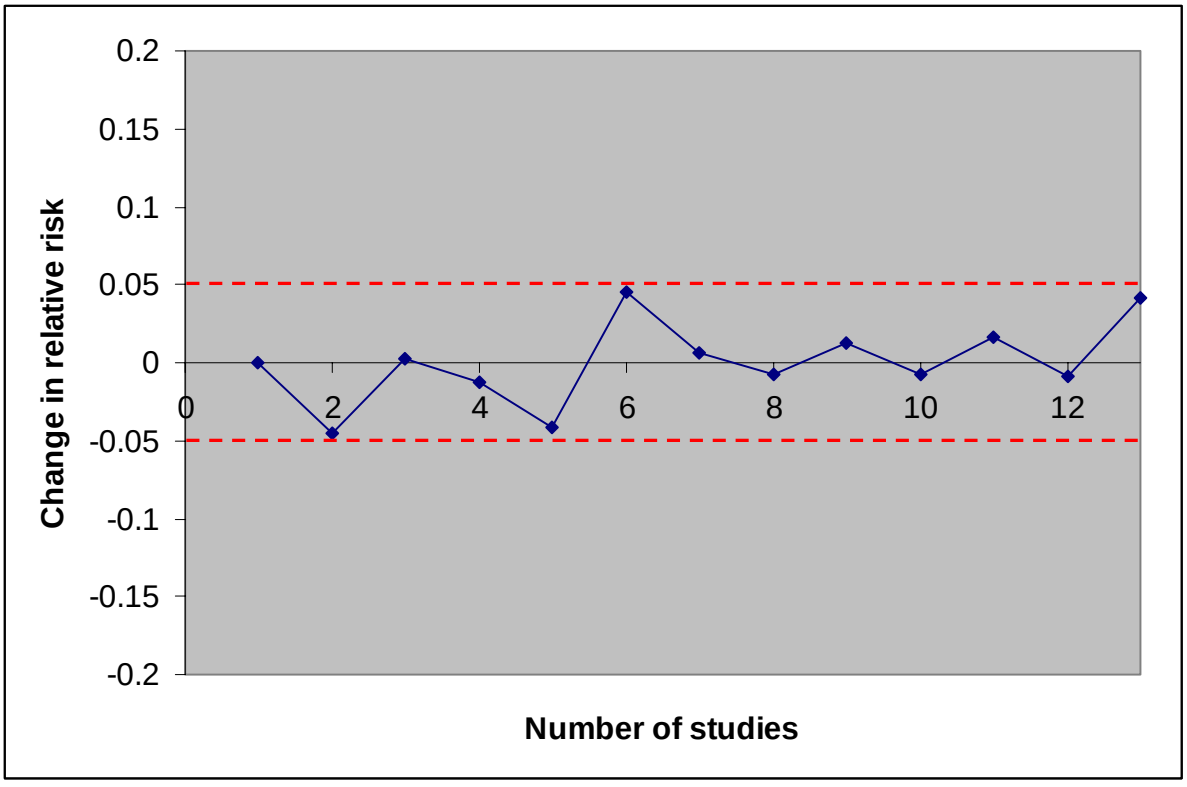


Figure I-6. Fixed-Effects Cumulative Meta-Analysis: Studies Added in Order of Increasing Study Quality

Study	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Crancer	1.190	1.010	1.402	2.079	0.038
Hansotia	1.235	1.083	1.408	3.150	0.002
Davis	1.232	1.081	1.403	3.135	0.002
De Klerk	1.244	1.095	1.412	3.358	0.001
Campbell	1.286	1.140	1.450	4.085	0.000
Stevens	1.241	1.107	1.390	3.716	0.000
Ysander (1966)	1.235	1.103	1.383	3.649	0.000
Waller	1.243	1.111	1.391	3.793	0.000
Eadington	1.230	1.100	1.375	3.632	0.000
Songer	1.238	1.108	1.384	3.764	0.000
Ysander (1970)	1.222	1.094	1.364	3.565	0.000
Cox	1.231	1.103	1.373	3.718	0.000
Laberge-Nadeau	1.190	1.082	1.309	3.576	0.000
	1.190	1.082	1.309	3.576	0.000





Appendix J: Systematic Reviews of RCTs that Assessed Safety and Efficacy of Treatments for Diabetes

Table J-1. Systematic Reviews of RCTs that Assessed Safety and Efficacy of Treatments for Diabetes

Reference	Organization	Organization URL	Document Specific URL	Treatment Class (Specific)	Document Type	Number of included studies
Is combination sulfonylurea and insulin therapy useful in NIDDM patients? Pugh J A, Wagner M L, Sawyer J, Ramirez G, Tuley M, Friedberg S J. A metaanalysis. Diabetes Care. 1992;15(8):953-959.	NA	http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME	http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-942624/frame.html	Sulfonylurea (Any in combo with insulin)	Systematic Review and Meta-Analysis	Unclear
Glimepiride: role of a new sulfonylurea in the treatment of type 2 diabetes mellitus. Campbell R K. Annals of Pharmacotherapy, 1998; 32(10), 1044-1052.	NA	NA	NA	Sulfonylurea (Glimepiride)	Systematic Review	8 trials
GLIMEPIRIDE. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=sulfonylurea	Sulfonylurea (Glimepiride)	Systematic Review	Unclear
NATEGLINIDE. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2001.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Meglitinide (Nateglinide)	Systematic Review	Unclear
Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. Brunelle R L, Llewelyn J, Anderson J H, Gale E A, Koivisto V A. Diabetes Care, 1998; 21(10), 1726-1731.	NA	NA	http://care.diabetesjournals.org	Insulin (Lispro)	Systematic Review + Meta-Analysis	8 trials
Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. DeWitt DE, Hirsch IB. JAMA 2003 May 7;289(17):2254-64.	University of Washington	http://www.uwmedicine.org/Facilities/UWMedicalCenter/	http://jama.ama-assn.org/cgi/content/full/289/17/2254?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=DeWitt&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT	Insulin (Various analogs)	Systematic review	

Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes: a systematic review and meta-analysis. Lawson M L, Gerstein H C, Tsui E, Zinman B. Diabetes Care, 1999; 22(Supplement 2), B35-B39.	NA	NA	NA	Insulin (Intensive therapy)	Systematic Review + Meta-Analysis	6 trials
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. Technology Assessment Report (project). . The National coordinating Centre for Health Technology Assessment (NCCHTA) 2004	National Coordinating Centre for Health Technology Assessment, UK	http://www.hta.nhsweb.nhs.uk	http://www.hta.nhsweb.nhs.uk/projectdata/1_project_record_published.asp?PjtId=1326&SearchText=Insulin	Insulin (Pumps)	Systematic Review and Meta-Analysis	20 trials
Continuous subcutaneous infusion of insulin with portable pump in diabetes type 1 patients. Pons J M V. Barcelona: Catalan Agency for Health Technology Assessment and Research (CAHTA), 2000. (IN01/2000) Available in English	Catalan Agency for Health Technology Assessment and Research (CAHTA) Esteve Terradas, 30. Edifici Mestral (1a planta) Recinte Sanitari Parc Pere Virgili 08023 Barcelona SPAIN	http://www.aatrm.net/html/en/Du8/index.html	http://www.aatrm.net/html/en/dir393/doc7921.html	Insulin (Pumps)	Systematic Review	Unclear
Economic evaluation of insulin lispro versus neutral (regular) insulin therapy using a willingness to pay approach. Davey P, Grainger D, MacMillan J, Rajan N, Aristides M, Dobson M. Pharmacoeconomics 1998; 13(3), 347-358.	Medical Technology Assessment Group (M-TAG), PO Box 5639, Chatswood 2057, Australia.	NA	NA	Insulin (Lispro)	Systematic Review and Meta-Analysis	6 trials
Efficacy of insulin infusion pumps. Impact on the quality of life of certain patients. IPE-00/27 (Public report). Amate Blanco J M, Van den Eynde A M, Saz Z, Conde Olasagasti J L. Madrid: Agencia de Evaluacion de Tecnologias Sanitarias (AETS), 2000. (Informe de Evaluacion de Tecnologias Sanitarias No.27) Only available in Spanish	Madrid: Agencia de Evaluacion de Tecnologias	http://www.isciii.es/aets	NA	Insulin (Pumps)	Systematic Review	Unclear
Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. Pickup J, Mattock M, Kerry S. BMJ, 2002; 324, 705-708.	Department of Chemical Pathology, Metabolic Unit, Guys, Kings, and St. Thomas's Hospitals School of Medicine, Guy's Hospital, London SE1 9RT, UK.	http://bmj.com	http://bmj.com/cgi/content/full/324/7339/705	Insulin (Pumps)	Systematic Review and Meta-Analysis	12 trials

Inhaled Insulin for the Treatment of Diabetes Mellitus. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2001.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Insulin (Inhaled)	Systematic Review	8 trials
INSULIN DETEMIR FOR DIABETES MELLITUS. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2004.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Insulin (Detemir)	Systematic Review	3 trials
Insulin Glargine for Type 2 Diabetes. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2004.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Insulin (Glargine)	Systematic Review	8 trials
Insulin Glargine: A Long-acting Insulin for Diabetes Mellitus. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2003.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Insulin (Glargine)	Systematic Review	8 trials
Insulin lispro: a critical evaluation. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1999.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Insulin (Lispro)	Systematic Review	13 trials
Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. *The Cochrane Database of Systematic Reviews* 2004, Issue 4.	NA	http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME	http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003418/frame.html	Insulin (monotherapy vs. Insulin and oral hypo)	Systematic Review and Meta-Analysis	20 trials
Insulin Pens Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=insulin+lispro	Insulin (Pen vs. Syringe) (Pen vs. Pump)	Systematic Review	20 trials
Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. Egger M, Davey Smith G, Stettler C, Diem . Diabetic Medicine, 1997; 14(11), 919-928.	NA	NA	NA	Insulin (intensified treatment)	Systematic Review + Meta-Analysis	14 trials

Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. The National coordinating Centre for Health Technology Assessment (NCCHTA)-2004	National Coordinating Centre for Health Technology Assessment, UK	http://www.hta.nhsweb.nhs.uk	http://www.hta.nhsweb.nhs.uk/execsumm/summ845.htm	Insulin (Glargine)	Systematic Review and Meta-Analysis	19 trials
Exenatide for the Treatment of Type 2 Diabetes Mellitus. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2005.	Canadian Coordinating Office for Health Technology Assessment. (CCOHTA)	https://www.ccohta.ca	http://www.cadth.ca/index.php/en/search?keywords=Exenatide	Glucagon-like peptide-1 (GLP-1) agonist (Exenatide)	Systematic Review	8 trials
Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: a meta-analysis of the randomised placebo-controlled trials. Johnson J L, Wolf S L, Kubadi U M. Archives of Internal Medicine, 1996; 156(3), 259-264.	NA	NA	NA	Combination therapy (Insulin and sulfonylurea)	Systematic Review + Meta-Analysis	16 trials
Is combination sulfonylurea and insulin therapy useful in NIDDM patients? A metaanalysis. Pugh J A, Wagner M L, Sawyer J, Ramirez G, Tuley M, Friedberg S J. Diabetes Care, 1992; 15(8), 953-959.	NA	NA	NA	Combination therapy (Insulin and sulfonylurea)	Systematic Review + Meta-Analysis	Unclear