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Isabelle Sanchez Date April 6, 2012

The Prevalence of Diabetes in Rural Areas of High-Income Countries: A Systematic Review and Meta-Analysis

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Abstract

The Prevalence of Diabetes in Rural Areas of High-Income Countries:
A Systematic Review and Meta-Analysis

By Isabelle Sanchez

Though diabetes is currently the fourth leading cause of death recognized among high-income countries (HICs), data from LMICs show that prevalence is growing rapidly in rural areas. Few studies have examined diabetes by residency location in HICs, suggesting possible underestimation. To understand the current magnitude and trends globally, the authors conducted an analysis of diabetes prevalence in rural areas of HICs by performing a systematic review of studies published from 1990 to 2011.

An extensive search of electronic databases (MEDLINE, Embase, Cochrane, CINAHL) yielded 1,513 eligible articles. Two independent reviewers screened studies based on objective protocol considering quality and homogeneity. Of the 171 articles fully examined, 32 articles were analyzed. To estimate the pooled rural prevalence of diabetes across HICs, a meta-analysis was performed; heterogeneity of samples was assessed via meta-regression.

A total of 97,478 persons in HICs generated a pooled rural diabetes prevalence of 9.6% (95% CI=8.3- 10.9), comparable by sex and age. Prevalence increased when grouped by 6-year intervals from 6.9% in 1990-1996 to 9.2% in 1997-2003 to 11.4% in 2004-2011. Of the 12 countries represented, the highest prevalence was found in Poland (17.2%; 15.5-18.9), USA (13.5%; 6.3-20.7), New Zealand (13.4%; 9.2-17.6) and Korea (12.8%; 8.0-17.6). Countries with the lowest prevalence were in Italy (4.8%; 1-8.6) and Sweden (4.4%; 3.6-5.3). By WHO region, the Americas had the highest prevalence (13.1%; 8.9-17.2), followed by Eastern Mediterranean (10.5%, 2.4-18.7), while Europe had the lowest estimate (8.3%; 6.3-10.3).

The widespread burden of diabetes prevalence in rural areas of HICs within the past two decades has escalated from 8.3% in 1985 to 13.7% in 2008 by study year. Re-prioritization of diabetes as a rural disease should be integrated into future research and interventions. For HICs, reducing diabetes prevalence can be a feasible target to minimize disparities, improve quality of life, and reduce economic burden in these regions.

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This thesis work originated from collaboration with an article on the global rural diabetes prevalence and comparing its epidemiological pattern between low- and middle-income countries and high-income countries (Zabetian A, Sanchez I, Ali MK, et al. *A systematic review and meta-analysis on rural diabetes prevalence globally—the gap between high- and low-plus middle-income countries narrows*). Prior to November 2011, the goal of that paper had been focused on examining high-income countries, but changed direction toward synthesizing and comparing both low-middle- and high-income country results. I worked in close collaboration with Dr. Zabetian from the start of that paper in June 2011 until November 2011 on all aspects: protocol development, conducting the search strategy, screening and selecting texts, and extracting data. From that data, I decided to continue with the high-income analysis where the previous paper left off as my thesis project, so there may be some overlap in ideas. However, I independently developed all written reports, tables, graphs, and analysis presented here for the purpose of this thesis.

I am extremely grateful to Dr. Zabetian's close guidance of this thesis project, especially for showing me how to approach the methodology, analyze the meta-analysis in STATA, and for referring relevant texts to understand the theory behind the pooled statistics and heterogeneity. The analysis from November 2011 to April 2012 was completely independent work by the thesis author, Isabelle Sanchez, and differs from that of the global rural analysis—also has a different overall goal and scope.

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BACKGROUND

The Global Impact of Diabetes

As one of the most frequently noted chronic disease burdens of modern society, diabetes mellitus (DM) has emerged as a public health epidemic. Diabetes is the fourth or fifth leading cause of death among high-income countries, accounting for 4.6 million deaths, (1) and 11% of healthcare expenditures among adults worldwide. Current estimates indicate that 8.3% of the world's population lives with this multi-factorial disease, and the number of people who have diabetes is expected to rise from 366 million to 552 million by 2030 (2)—approximately three new cases every ten seconds, leading to ten million persons developing diabetes annually (2). However, we exceed prevalence projections faster than we can update them.

Current Knowledge and Contributing Risk Factors

The rampant obesity pandemic is a major risk factor for diabetes, as are increasingly sedentary lifestyles and high-caloric diets that often accompany fast-paced urban living (16). Shifting clinical focus from treatment to prevention has led to improved surveillance and higher sensitivity diagnostic screening, which accounts for sharp increases in reported diabetes trends since 1990 (13, 16, 95). Rising global diabetes trends have simultaneously led to increases in health conditions that decrease work productivity, diminish quality of life, strain communities and stress an already burdened health system. This epidemic of diabetes requires improved, sustainable, long-term prevention strategies that consider its latent onset. Diabetes, as a universal health issue, should be a concern for rural areas as well, due to these individual predispositions exacerbated with environmental risk factors. Poor access to routine primary care or minimal availability of resources to improve diet, promote healthy lifestyles or increase physical activity—factors that negatively impact diabetes risk—are typically observed in rural areas.

With modern epidemics transitioning from infectious to chronic diseases, diabetes has become an emerging condition typically characteristic of high-income countries and urban areas (14). However, recent literature confirms that diabetes is no longer restricted to urban areas; it also similarly affects low- and middle-income countries (4, 16). Since all rural areas have similar socioeconomic disparities, regardless of geographic location, it is reasonable to conclude that these patterns also pertain to high-income countries. Notably, the United States and Japan are among the top ten territories identified to have the greatest number of diabetic adults globally (2). Previous studies in developed countries have focused on estimating the burden of diabetes in urban settings and generalizing findings to the entire country; however, it is suspected that current published statistics may actually underestimate diabetes prevalence in rural areas (3, 95).

Gaps in Knowledge among Rural Regions of High-Income Countries

It is questionable whether current statistics accurately reflect the burden of diabetes in rural areas. An article by Lee and colleagues shows the need for consistent, valid results and concludes that the prevalence of diabetes is higher in rural than in urban populations of Korea (5). Al-Nozha, et al. reported comparable findings in rural America, with an increasing trend toward higher prevalence rates encompassing the elderly population (6). Conversely, a study by Melidonis acknowledges prevalence variations among Greeks who tended to have higher proportions of diabetes in urban areas when compared to rural areas, further raising uncertainty of diabetic trend accuracy among high-income countries (9). Estimates of diabetes in the literature differ between studies within the same given country, when comparing urban and rural populations. There is no clear conclusion if there is a significant difference in diabetes prevalence between these two areas in high-income countries (16, 95). Furthermore, when examining individual population prevalence for a rural area, estimates vary without an overall definitive exploration of why. It is, therefore, unknown how detrimental the current burden of diabetes is in rural areas of high-income countries. Additionally, it is suspected that discrepancies reflect poor

trends in obesity and more sedentary lifestyles, but it is unclear whether certain populations are comparable for an overall summary prevalence estimate of diabetes in these regions (9). The variation among published studies may also result from no singular definition of "rural" areas (8). Nevertheless, there is a need for more reliable estimates for understanding true diabetes burden, with the larger goal to increase utilization of preventive health care in response to this debilitating health problem (10).

Considering these implications, additional literature suggests that populations within rural areas of high-income countries are changing, ultimately affecting social determinants of health (16, 95). Compensating for the fast-paced lifestyle needed to meet the demands of rapidly growing populations with additional goods and services, high-income countries are nationally expanding economic growth and urbanizing previously rural areas (12, 13). Among previous studies examining rural areas, urbanization has been credited as one of the major contributors to this diabetes epidemic (7). A study in Greece recognizes the prevalence variation among a previously agricultural population, resulting from changes in living conditions and socioeconomic status (9, 11). With these rapid changing predictors in lifestyle, severe diabetes prevalence is a high possibility affecting these regions. Despite improvements in global economies, diabetes continues to plague expanding populations, a trend that will persist unless targeted interventions are effectively disseminated.

If suspicions about diabetes estimates are found to more adversely affect larger proportions of rural populations than expected, then our prevention efforts must become less fragmented and reactionary, but rather, should be more collaborative and strategically proactive to include these regions. Several studies provide quantitative evidence suggesting that rural areas need more medical and political attention. For example, average random blood sugar levels were found to peak higher and earlier than urban areas, suggesting a more severe onset of diabetes earlier and that rural inhabitants were living with diabetes for a much longer part of their lifetime (12). The national rates of some studies in high-income countries reflect a large magnitude of the

disease in communities and allude to a gap in risk factor control by the general population or from healthcare services (12). The evidence needed to direct attention toward diabetes in high-income countries will support public health policies in rural areas, ultimately mitigating health disparities affecting these regions. Since there are fewer rural areas within high-income countries, policies and interventions may be more impactful in these areas—as feasible targets for glycemic improvement interventions for the nation and for appropriate health resource allocation.

The Need for Pooled Prevalence of Diabetes

As such, national and local governments may be unaware of the true magnitude of diabetes within their country or region and even more unaware how its growing trends could impact their society's health and economy. Having reliable estimates of the diabetes presence in the world and by region will further justify how rural areas in high-income countries may collaborate to decrease associated risk factors and increase protective factors with innovative strategies. If all rural areas of high-income countries have comparable estimates leading to commonly discovered etiologies, then strategic areas for improvement could be appropriately targeted. Accurately assessing the trend of how diabetes prevalence has changed over time, therefore, will provide needed clarity on how the diabetes has affected rural areas. With population growth, this disease burden will only continue to escalate and, thus, updated assessments are necessary to fully understand all facets of the disease—socially, culturally and medically.

The most cost-effective method of aggregating all worldwide diabetes prevalence results into an overall summary estimate is the most impactful and helpful resource to prioritizing interventions and emphasizing importance of strengthening diabetes prevention programs. Organizing results and summarizing to a pooled estimate of diabetes prevalence by region will create meaning for stakeholders beyond the scientific community. To complement previous explorations of prevalence within low- and middle-income countries (4), a meta-analysis on rural

areas of high-income countries is the most feasible, cost-effective, and useful option to raise awareness of the severity of the diabetes epidemic to society.

Therefore, to estimate the overall prevalence of diabetes in rural areas of high-income countries, we performed a systematic review of the literature between 1990 and 2011. Heterogeneity of populations involved in estimates was thoroughly evaluated to obtain the most accurate estimate. To date, a systematic review of this nature is the first of its kind. Aggregated data from this detailed analysis will provide clarity of current diabetes burdens in countries that have previously reported multiple within-country estimates. Regions with similar economies will be able to work together and develop similar effective interventions within rural regions. Thus, rurality may be considered as a priority area to focus on within the diabetes pandemic, as it has been previously overshadowed by an urban-associated epidemic.

METHODS

Search Strategy

Biomedical and healthcare journal databases were searched to find all relevant articles on the prevalence of diabetes in rural areas of high-income countries published between January 1990 and August 2011. The databases used involved the National Library of Medicine's Medical Literature Analysis and Retrieval System (MEDLINE), Elsevier's EMBASE, Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) through EBSCO Publishing. The search strategy used a combination of MeSH and free text terms "diabetes mellitus", "prevalence" or "epidemiology" or "morbidity", "rural" and the "[high-income countries]" (Figure 1). The terms were selected in order to capture all potential articles related to diabetes prevalence and to remain unbiased, especially when classifying a rural setting.

The high-income countries included for this review used categories defined by the World Bank country economies using a criteria of those with a GDP per capita of $12,276 or more (Table 1) (21). Included articles must have defined their population as rural by their own classification stated clearly within the article. No restrictions were placed on the language of the articles, as appropriate translators were used for those not in English: Spanish (I.S.), German (M.H.), and Japanese (C.A., S.H.).

References of related review articles were manually examined and experts were contacted experts in the field in order to find and include additional articles. The search was later updated to include articles not in the initial examination. Methodologically, the PRISMA guidelines for observational studies were followed (22). A reference manager was used to organize articles for review (EndNote Library, Version X4, CA).

Study Selection

All possible articles were collected from the four databases, manually considered by examining bibliographies of relevant articles, and by suggestions of experts. Two independent reviewers (A.Z., I.S.) selected eligible articles from the initial search based on predetermined selection criteria. Duplicates were removed and then all remaining articles were screened by title and abstract. Articles that were excluded at this first stage fulfilled at least one of the following criteria: 1) Only explored diabetes type 1, uncommon forms of diabetes, or gestational diabetes; 2) Did not contain the outcome of diabetes prevalence; 3) Did not examine a rural area; 4) Were not conducted in a country defined as high-income as defined by the World Bank; 5) Non-original research (conference abstracts, editorials, letters, or commentaries); and/or 6) all studies conducted on a specific group not representative of the population (i.e., ethnicity, gender, occupation, socioeconomic, disease state). Eligible articles were selected with outcomes of diabetes prevalence in rural areas in high-income countries. Disagreements between the reviewers were resolved by consensus after consultation with a third author (M.A.).

After the first round of exclusion, the remaining articles were examined in a detailed review utilizing the full-texts of articles. Investigators fluent in the foreign language of an article not in English were used to translate the information directly. Additional articles were derived from country-specific diabetes experts for further review. Only those articles using objective standard criteria, such as those established by the World Health Organization (WHO) or the American Diabetes Association (ADA), to define diabetes were used for ensuring uniform cut-points. Studies that did not use a random sample of the population were excluded.

Those reviewed by full-text were excluded based on the same criteria utilized in the preliminary screening plus consideration of self-reported diagnosis of diabetes. If more information about study methodology was required, the article authors and were contacted for clarification. In order to avoid using the same population twice from different studies, we further

refined the included studies at this final stage. The final studies used for analysis of diabetes in rural regions were of the highest quality, as determined by an objective quality score.

Data Extraction

Data was extracted from the final selected studies by using standardized protocol that was developed by the authors (I.S., A.Z.). Diabetes indicators were obtained from each study in addition to a number of factors to describe the study population (such as age and gender proportions), area of study, definition of diabetes used, and how rural was defined for study purposes. When there were articles utilizing the same dataset for a specific population, the article that contained the most relevant and recent information was used. All data was extracted by one author (I.S.) and reviewed by a second author (A.Z.).

Quality Assessments

The included articles for analysis were limited to high-quality ones by assigning a quality assessment score to each study. Those studies scoring a quality score of 2 or greater were included (4). This measure was taken to maximize the strength of accurate prevalence estimates used and to ensure that the studies included were as similar as possible. The study quality indicators considered were as follows: 1) high representativeness of the study sample to the national population; 2) objective methods of diagnosing diabetes; 3) use of appropriate statistical methods; and 4) minimal non-response bias.

National representativeness was determined by an examination of whether the cohort was sampled in a localized rural region or if from multiple random rural areas across the entire country. In regards to non-response bias, if at least 75% of the sample approached contributed data for prevalence results, it was determined there was minimal non-response and the study earned a quality indicator score. Objective methods of diagnosing diabetes were those standardized methods of diagnosing diabetes separate from subjective classification by an

investigator or subjective self-report. Appropriate statistical methods were those defined as appropriately reporting proportions of diabetics among population of rural study or the appropriate diabetic prevalence calculations.

Related Issues

Standard definition of diabetes varies by WHO and ADA criteria (Table 2)

All studies eligible for final abstraction used the standard definitions for diabetes as defined by the WHO and the ADA based on objective blood glucose cutoffs (Table 2) (20, 23, 24, 25). The glycemic categories used by the studies involved both the old and new WHO criteria; however, the blood glucose cutoffs changed from 1985 to 1999. Studies in this review also could utilize the ADA criteria either in 1997 or 2003, since they are equivalent with the 1999 WHO criteria and the cutoff values remained constant during these dates.

Articles have recognized that this change in blood glucose cutoffs from old to new WHO criteria could allow for a change in prevalence results, so it is an important issue to consider when comparing diabetes proportions among varying time periods (6). Additionally, the values may differ between venous blood glucose in comparison with capillary glucose measurements. Both of these types of methods to categorize diabetes are further defined by the WHO and ADA standardized guidelines. Given these heterogeneous methods to identify and classify diabetes status, we conducted sensitivity analyses to evaluate if the prevalence of diabetes in rural areas was affected by these differences in methods of assessment.

Analysis Plan

Standard meta-analysis procedures were used to estimate the pooled prevalence of diabetes in rural areas of high-income countries. Methods for estimating variance between the individual studies were performed by using a random effects model. In this way, data was analyzed with the assumption based on studies random of some hypothetical population of studies

(17). The Der Simonian-Laird method was used, based on a random-effects assumption because some heterogeneity is a possibility among global high-income countries. The proportion and crude prevalence of people with diabetes from each study were pooled with the overall population to calculate standard errors and overall resulting diabetes prevalence. To display a trend of prevalence estimates, the analysis was stratified by publication year or study year. Only those studies in countries that fit into six-year categories were used for this display. All data were analyzed using STATA 11.1 (College Station, TX), as this provides the most comprehensive software for meta-analyses capabilities.

To statistically test for homogeneity, the variation of prevalence magnitude between studies was measured with the I^2 index. If studies are determined to be homogenous, then the assumption of a random-effects model will hold true and impose stronger validity on the overall pooled diabetes prevalence (17). When the sample size of the individual included studies exceeds 20 participants, this test for homogeneity has reliably more power than other methods of assessing homogeneity. Cutoffs from the Higgins and Thompson criteria deemed a pooled result as having high levels of heterogeneity if an I^2 value was found to be greater than 75 or a medium level of heterogeneity if an I^2 value was greater than 50 but less than 75.

A meta-regression analysis was used to understand the drivers of heterogeneity found between included studies. The characteristics used as variables within individual studies were considered in a multivariate regression analysis, where the prevalence estimates were the dependent variable and the characteristics—including study design or measure of values for subjects within the studies, such as mean age or gender—were the independent variables (17). Variables included in this model were sex, mean age, study end year, influence of the 1997 change in diagnostic criteria by WHO, and study quality covariates (appropriate statistical methods used, non-response bias, and national representativeness). No collinearity was anticipated between these variables, but was examined to ensure that it was not a problematic in our model. Studies were categorized into groups (Table 2): those that based diagnosis on the older

fasting plasma glucose criteria prior to 1997 at 7.8 mmol/L and studies that used the diagnostic criteria after 1997, which is the current threshold of 7.0 mmol/L and/or 2-hour post-challenge glucose level of 11.1 mmol/L (20, 23, 24, 25). The study quality covariate of objective data collection methods was not included in the model because all studies analyzed in the review had a strict requirement of having standardized blood draw methods and glucose estimations, as specified by the WHO and ADA. The inclusion of this factor would have caused unnecessary collinearity problems since data is being repeated. We hypothesized that the studies would have some minimal heterogeneity, but overall would remain homogenous due to our streamlined inclusion criteria and high-quality measures.

An analysis to assess heterogeneity helps to identify some bias, but additional assessments can be performed graphically to objectively assess additional bias among studies and results. The Gailbrath plot for heterogeneity was used to assess bias as a statistical test of asymmetry. Since individual data was examined in this method, greater comparability between studies could be observed (18). Therefore, studies found to impact results through bias were removed from the analyses and compared to results with all possible studies included.

Sensitivity analyses were conducted in order to determine if the prevalence differed based on certain factors. This methodology evaluates stability of our analytical conclusions from the assumptions initially made for the analysis (17). Questionable studies were excluded from an analysis of prevalence to determine if these factors dominated the study results in an underestimation or overestimation of the calculated pooled prevalence. Certain studies were excluded considering differing eligibility criteria or cut-offs for inclusion, such as comparing the old and new WHO and ADA glucose designations.

A Forest plot was created for all the studies to visually compare the study results overall and by specific region. Six geographic areas, specified by the WHO, grouped the high-income countries from which studies were included: Africa (AFR), the Americas (AMR), Eastern Mediterranean (EMR), South-East Asia (SEAR), and WPR (Western Pacific) (19). Table 3

provides a list of countries included in these specific regions. Forest plots also grouped studies by publication year classifications by seven-year periods: 1990 to 1997, 1998 to 2004, and 2005 to 2011. Additionally, diabetes prevalence was displayed on a Forest plot which grouped estimates by the year studies were conducted rather than when published. For this, five-year periods were specified: 1985 to 1989, 1990 to 1994, 1995 to 1999, 2000 to 2004, and 2005 to 2008. However, only 27 studies (85%) provided information on study start or end year. Considering the year that the study ended can provide a better idea of when the study data was abstracted and what time period the results reflect.

RESULTS

Search Results

Initially, from the search using key terms, there were 1,513 articles collected from all databases, manually considered by examining bibliographies of relevant articles, and by suggestions of experts. After excluding 253 duplicates, there were 1,119 articles additionally excluded by screening title and abstract.

One hundred seventy-one articles warranted a detailed full-text review. At this stage, 4 articles were derived from country-specific diabetes experts for further review. From those reviewed by the full-text article, 143 additional studies were excluded due to the same criteria utilized in the preliminary screening plus consideration of self-reported diagnosis of diabetes (Figure 2). Nine studies required more information from the article authors and were contacted for clarifications. Four authors provided additional information upon request, but only information from two authors qualified the studies to remain in the review. The remaining seven studies were not used due to lack of relevant information, if the authors indicated that they no longer had access to the study data, or if the authors did not respond to our inquiries. The 32 studies in rural regions chosen for our final review analysis were of the highest quality, as determined by an objective quality score.

Study Characteristics

Thirty-two studies were analyzed to derive an overall pooled estimate of diabetes prevalence among rural areas of high-income countries (Table 8). Information from 93,091 subjects was used to infer these estimates, with sample sizes ranging from 65 to 26,472 individuals. Twenty-five of the selected studies were cross-sectional studies and eight were cohort studies. Twelve high-income countries were included in the review.

Most of the studies were from WPR (16 studies, 50%), when considering WHO region. EUR had the next greatest amount of studies accounted for (10 studies, 32%), followed by EMR (3 studies, 10%) and AMR (3 studies, 10%). No high-quality studies were found from rural areas of high-income countries within AFR or SER. By specific country, Japan had the greatest number of studies included in our review (7 studies, 22% of included studies), followed by Korea (4 studies, 13% of included studies), and then Australia (4 studies, 13% of included studies).

Pooled Estimates of Diabetes Prevalence

Meta-Analysis

Overall from 1990 to 2011, the pooled prevalence of diabetes among rural areas of high-income countries was found to be 9.6% (95% CI, 8.3 to 10.9%) (Table 4). The analysis revealed significant heterogeneity across studies ($I^2 = 98.2$, $p = 0.001$). Pooled prevalence estimates varied significantly by year in which study was conducted ($p = 0.046$), but not by sex ($p = 0.778$) or sample national representativeness ($p = 0.992$). When considering a rough general trend by year when study started, the rural prevalence of diabetes increased from 8.3% (95% CI, 6.8 to 9.8%) before 1990 to 13.7% (95% CI, 10.3 to 17.1%) during the period of 2003 to 2008 ($p < 0.001$) (Table 5, Figure 5). Pooled prevalence estimates also varied by year study was published, increasing from 6.9% (95% CI, 5.1 to 8.8%) during the 1990 to 1996 period to 11.4% (95% CI, 9.1 to 13.2%) during the period of 2005 to 2011 ($p = 0.036$) (Table 6, Figure 6).

The geographic location of studies was also significantly associated with the variability of rural diabetes prevalence rates among high-income countries ($p < 0.001$). When considering WHO region, the stratified results of rural diabetes prevalence were found to be greatest for the Americas at 13.1% (95% CI, 8.9 to 17.2%), followed by Eastern Mediterranean at 10.5% (95% CI, 2.4 to 18.7%) and lowest for Europe at 8.3% (95% CI, 6.3 to 10.3%). Studies within the Americas group remained the least heterogeneous ($I^2 = 85.5$) while Eastern Mediterranean studies

were the most heterogeneous from each other when considering rural diabetes prevalence (I^2= 98.2).

Table 4 reports results by country over the period of 1990 to 2011. The diabetes prevalence varied from a range of 4.4% (95% CI, 3.6 to 5.3%) in Sweden to 17.2% (95% CI, 15.5 to 18.9%) in Poland. Other notable countries with high rural diabetes prevalence results were USA at 13.5% (95% CI, 6.3 to 20.7%), New Zealand at 13.4% (95% CI, 9.2 to 17.6%), and Korea at 12.8% (95% CI, 8.0 to 17.6%). Notable countries with lower diabetes prevalence results in addition to Sweden were Italy at 4.8% (95% CI, 1.0 to 8.6%) and Japan at 7.0% (95% CI, 5.6 to 8.5%).

Exploring Heterogeneity

Meta-Regression Analysis

Since geographic region and year were significantly associated with prevalence, they were included in the meta-regression model along with suspected influencing variables of sex and sample national representativeness (Table 7).

A multivariate meta-regression backward stepwise model using Europe for the comparison group yielded similar findings. The proportion of the sample population that was male, national representativeness, and publication year were all not significantly associated with prevalence rates (Table 7). The meta-regression analysis revealed that the study publication year did not increase the pooled prevalence of diabetes by 0.3% (97). Quality covariates were considered from a univariate analysis, but none deemed significant for inclusion in model except for national representativeness. Since there was not ample information on mean age from all studies, it was not considered in the model. Therefore, there were no variables determined to impact pooled prevalence in any aspect.

Sensitivity Analyses

To test whether the sources of heterogeneity made an impact on the overall findings, factors of particular concern for influencing the estimated pooled prevalence results of diabetes in rural areas of high-income countries were examined. Several sensitivity analyses were performed assessing impact of older WHO guidelines, diagnostic methodology, demographic factors, and eligibility criteria such as study quality.

The Galbraith Plot revealed the three most heterogeneous studies: Ohsawa et al., Al-Nozha et al., and Matusmoto et al. (6, 26, 27). These results were excluded during the sensitivity analysis, providing a pooled prevalence estimate of 9.6% (95% CI, 8.4 to 10.9). The removed studies did not significantly influence the prevalence result, but did decrease the between-study heterogeneity from 98.2% to 97%.

To consider the discrepancies between the adjusted guidelines to the WHO criteria fasting plasma glucose made during 1997, a sensitivity analysis was performed to assess how this factor could have impacted our pooled prevalence results. The old and new ADA guidelines for diagnosing diabetes remained unchanged at a value of greater than or equal to 126 mg/dL, but the WHO definition adjusted the fasting plasma glucose cut points from greater than or equal to 140 mg/dL in the old criteria to greater than or equal to 126 mg/dL. A suspected over-estimation of the results was confirmed when a sensitivity analysis excluding 12 studies using the old WHO criteria yielded a prevalence of 10.5% (95% CI, 8.6 to 12.4%). Therefore, one should interpret our pooled prevalence results understanding the change of guidelines in 1997 and a slight inflation of prevalence in earlier reports.

In order to assess the impact of narrowed FPG criteria in diabetes diagnoses, another sensitivity analysis was performed. It was suspected that those studies using only FPG or 2-hour plasma glucose in their methods for diagnosing diabetes might underestimate the pooled prevalence results since not all of the possible diabetics in the rural population may have been accounted for. Studies that only used one of the two possible methods for assessing glucose levels

were excluded for this sensitivity analysis, leaving 15 studies that used both diagnostic methods. The pooled prevalence of diabetes using both FPG and 2h PG methods was found to be 8.1% (95% CI, 6.7 to 9.6%), lower than expected—suggesting that studies using only one method are subject to include more persons than actually have diabetes than by using a reinforced diagnostic method with two assessments to consider. However, since sampling may not truly account for all possible diabetics within a study's given area, this suspected overestimation of using one method rather than two methods in diagnosing diabetes should have a minor overall effect on the results.

When sex and age were incorporated in a sensitivity analysis to examine heterogeneity, the pooled prevalence results remained unchanged. For the 21 studies that included prevalence by sex, the pooled prevalence remained similar for men (8.2%, 95% CI, 7.1 to 9.3%) and women (7.8%, 95% CI, 6.5 to 9.1%). For examining the influence of age, only 16 studies had information on the mean sample age. Thus, a sensitivity analysis was performed a more inclusive age range provided by studies. All 34 studies had information on age in some capacity, but 7 studies were excluded with subjects greater than or equal to 40 years of age, yielding an unchanged prevalence estimate of 9.2% (95% CI, 7.9 to 10.6).

The influence of study quality on pooled prevalence results was also assessed. The prevalence was calculated with studies meeting all four quality indicators, yielding 9% (95% CI, 6.0 to 11.9%) from three surveys. For examining individual quality score effects, a sensitivity analysis was used excluding 10 studies with non-response bias determined that no significant difference was found from the calculated pooled prevalence result at 9.9% (95% CI, 8.3 to 11.5%). When considering the three studies with a nationally representative rural sample, the prevalence estimate remained unchanged at 9% (95% CI, 6.0 to 11.9).

DISCUSSION

Results support the finding that diabetes is currently a high-burden disease among rural areas of high-income countries, suggesting a possible area to strategically expand diabetes intervention efforts for national improvement. The pooled prevalence of diabetes in rural areas of high-income countries was found to be 9.8% (95% CI, 8.6 to 11.1%)—greater than the current world estimate of 8.3% and even greater than that of rural areas within low- and middle-income countries at 5.7% (2, 4). This is of particular concern since cultural, social and economic differences make rural populations more susceptible to a greater risk of chronic diseases and complications, impacting productivity, incurring escalated costs and diminishing quality of life to further differentiate the health of rural areas from that of its urban counterpart.

The diabetes prevalence in rural areas of high-income countries within the past two decades has risen steadily from 6.9% in 1990 to 10.8% in 2011, with no difference seen between males and females. When considering study start year, the burden of diabetes on rural areas of high-income countries doubled over the past 23 years—an increase from 7.9% in 1985 to 14.7% in 2008. Rural prevalence was greatest in the high-income countries of Poland, USA, and New Zealand and the lowest among Denmark, Sweden, and Italy. By region, the Americas had the highest prevalence at 10.3% and the lowest from Europe at 5%. Socio-economic and lifestyle contributions of these regions can account for these observed differences between regions. Examples of these contributions are decreased access to primary care or normal sources of care, fragmented policies, and health initiatives, and limited health literacy of the generalized population, among many others.

These pooled results are consistent with other literature examining diabetes prevalence results among rural areas, but highlight the most important aspects concerning rural regions by geographic economies. The pooled diabetes prevalence helps synthesize the most impactful studies from a wide variety of areas, explaining diabetes burdens and identifying areas to place

interventions. These results provide a new perspective on diabetes prevalence globally: Contrary to what one would assume, rural areas in high-income countries have an increased diabetes burden that may be similar to that of their urban neighbors.

Several underlying causes can account for this strong magnitude of effect. Recent demographic change in rural communities, such as income level, education, and health insurance availability puts these residents at a higher risk of diabetes. Previous physically labor-intensive lifestyles—such as farming—associated with rural living have now decreased, with an adoption of advances in technology, thus causing more sedentary activities (15). Also, there may be low awareness about diabetes and risk factors among rural inhabitants, since health marketing and regular access to primary care may not warrant opportunities for diabetes education (96). Perhaps resulting from gaps in care, lack of regular follow-up may allow for a large proportion of the rural population to be unaccounted for in previous diabetes estimations. In addition, less access to fresh markets may induce poor habits of consuming fast-food meals as the only convenient and affordable options in a regular diet for rural persons (29). Future research should investigate rural areas as target populations for glycemic improvement in order to advance health, quality of life, and reduce the health and economic burden of diabetes in these regions (30).

The rural diabetes prevalence of high-income countries in this review appears to be increasing in line with the rising trend of obesity and is suggestive of world population aging, urbanization, and lifestyle changes (15). The global shift towards urbanization may have accounted for sparse data in rural regions and thus a higher reported prevalence. Currently in high-income countries, the International Diabetes Federation (IDF) reports that twice the amount of people live in urban than rural areas (2). In addition, the number of people living and working in rural areas is decreasing (16). Younger populations are more likely to migrate from rural to urban areas in order to seek employment and education, leaving older populations at home (29). Though, we have not seen improved focus on these rural areas, public health efforts should not

falter. As high-income countries suffer from a large burden of diabetes, it is important to strategize how to best reduce the number of persons developing diabetes.

Strengths

One of the strongest components of this study was that it was as comprehensive as possible in acquiring and considering eligible studies for analysis. In order to maximize the amount of studies included and minimize selection bias, four different biomedical databases were thoroughly searched, a review of the references from each included article were examined, and experts native of our included high-income countries were contacted to find as many relevant high quality studies as possible in every included region. This also means not limiting any global region by language barriers or journal type. Native speakers trained in medicine or public health appropriately translated all foreign language articles, where only one of these studies met the inclusion criteria. Therefore, this review has confidently considered all of the available articles available on diabetes prevalence in rural areas of high-income countries.

To decrease heterogeneity between included studies, we utilized strict criteria of standardized diabetes definitions articulated by the WHO and ADA, which is used universally to clinically diagnose diabetes. Self-reported indications of diabetes were not considered for inclusion. Since studies often used multiple methodologies to assess blood sugar levels, thorough examinations of the devices, procedures, and blood sample types were used to better understand the classification process and relate it to heterogeneity between studies. In this way, misclassification was reduced and a reliable estimate of prevalence was obtained as our result. To further verify homogeneity, statistical tests were performed to ensure that the studies were measuring somewhat equal effect sizes based on study design or study characteristics (17). From this and additional sensitivity subgroup analyses, we found that the models yielded similar results when taking these factors into account.

It is important to note that the blood glucose cutoffs changed in criteria from the old definition used by the WHO in 1985, until updated in 1999. The ADA followed the same blood sugar cutoff levels in 1997 as in 2003. Having different cutoff levels can change prevalence estimates and thus affect our overall prevalence results when considering older studies. Thus, a sensitivity analysis was used to ensure no difference between those who used older criteria from those who used newer criteria, showing that the difference in criteria accounted for slightly inflated results. This can be explained by earlier studies using the WHO 1985 criteria with less strict blood glucose cutoff criteria for classifying participants as diabetic, thus accounting for a larger number of diabetics than truly present in the population. Since sampling of populations may simply not capture all possible rural inhabitants with diabetes, our calculated pooled prevalence is still likely an underestimation of the true overall prevalence among rural areas. Additionally, the use of a random-effects model will generally yield a confidence interval at least as wide as or usually wider than the confidence interval based on a fixed-effects model, so it is generally a more conservative approach (17).

Additional sensitivity analyses on other questionable factors affecting our pooled estimate ensured that there were no differences between certain groups analyzed. No differences were found in results by gender or age, indicating that neither exemplified a greater burden of diabetes and these were not confounders of our overall estimate. Prevalence estimates were stratified by study start year and end year to account for lag times in study publication. By examining trends of all possible studies over a large span of time, we can observe an increase in interest directly aligning with the increase in prevalence trends since 1990. Most of the studies included were published within the past 5 years rather than evenly spread throughout 1990, which reflects the most current estimate of diabetes burden within these areas.

This meta-analysis was the most cost-effective approach at determining the magnitude of diabetes within a suspected affected rural area and covered a large scope of communities within high-income countries. The utility of combining the highest-quality articles on diabetes

prevalence among all rural areas of high-income countries interprets results to provide meaningful value and application to society. These simplified results can extend to groups beyond the researchers and be extrapolated to create awareness of diabetes problems to the general public. Not only can this information be integrated into future public health and clinical strategies, but also, rural communities can proactively relate to these summary statistics with lifestyle adjustments individually. In addition to the information being useful to community members, the impact of benchmarking comparisons and clearly stating the statistics within digestible communications—such as pamphlets, television ads, and reports in the literature—will be very impactful. This will ultimately support the Institute of Medicine's push to increase health literacy through culturally appropriate means.

Limitations

Systematic reviews are recognized to provide results with limitations, so results should be interpreted and implemented with caution. A variety of methods were used to account for bias and improve the high quality, comparable data obtained for analysis. However, this review was unable to investigate areas where there were few high-quality studies. Since there is a well-defined gap in research and a lack of reliable data on diabetes prevalence within rural areas in high-income countries, we were unable to find high-quality studies on rural diabetes prevalence in some countries that play active roles in contributing to diabetes prevalence since there were no high-quality articles. This can be partly explained by limited rural areas within these countries not included, such as Singapore (31).

Perhaps the largest cause of unavailable literature among rural areas is due to the fact that there is currently no consensus on a definition to classify rural areas. Despite the fact that economies are constantly fluctuating and the urban-rural dynamic continues to expand towards urban, the definitions of rural and urban have accommodated to time and vary by location. In order to not limit some high-quality articles due to the ambiguity of a rural definition, a less strict

inclusion criterion was used in which studies self-identified rural populations within their study. Over half of the studies included in the review had an unclear definition of "rural" and did not differentiate how populations were "rural," other than specifying that the population under review was rural. Other common themes of rural definitions within studies involved using quantitative population cutoffs, assessing distance from an urban center, indicating that a majority of inhabitants depended on agriculture for employment and lifestyle, or using a ratio of local health care facilities to persons or geographic area of coverage. Since these classifications varied from study to study, a sensitivity analysis could not be performed. Furthermore, without a standard definition, populations used could be subject to misclassification or selection bias during screening. However, since there was a non-specific definition of rural for inclusion in the review, our results may be generalized to other rural areas of high-income countries by region because it is likely not to limit any rural area globally.

Since many studies included in the review failed to specify the type of diabetes being examined, the results may be generalized to all persons with diabetes rather than those with type 2 only. Articles that only studied type 1 diabetes were always excluded when specified as the sole contributor to prevalence. Not having results tailored to a specific type of diabetes can allow for extrapolation of results to the generalized rural population of high-income countries and to those not already accounted for. Therefore, greater utility can come from the results than previously predicted, as type 2 diabetes accounts for a majority of these cases because it is more prevalent (2).

Future Directions

The large magnitude of results and increasing prevalence trend exemplifies a need for future research efforts focusing on interventions in rural areas of these high-income countries. Cost-effective routine diabetes care, such as early screening, metabolic control, and monitoring of modifiable risk factors is important as well as improving access to rural health centers. In

addition, diabetes education for both diabetic and overall population of rural areas will be helpful to reduce escalating rates of diabetes in these areas. Further research is needed to determine if there will be a similar trend observed among the urban areas of those countries in our review.

A universal definition is needed to further explore rural results and develop strategies to control diabetes specific to these areas. If more research is to be done to explore this area, then having a set idea of the population type will streamline prevention efforts. Along these lines, having more high quality studies available in more rural regions of high-income countries can more accurately determine the burden of diabetes in rural areas and projections can be calculated to further ensue focused prevention and intervention efforts. Ongoing routine surveillance will be key to successful estimates and assessing future projections. Additionally, comparing urban and rural diabetes prevalence statistics can more specifically streamline diabetes strategies in areas of overlap and help direct future funds to reduce overall national diabetes prevalence. It is important to find and develop feasible interventions to improve diabetes in rural areas of high-income countries. Programs showing promise in significantly improving diabetes outcomes within high-income countries can serve as a model for low- and middle-income countries to follow shortly after.

Future studies can consider adhering to a strict definition of diabetes, such as the WHO or ADA criteria. Conducting studies involving national random samples with a wide variety of rural populations can allow for an improved estimate of diabetes prevalence in that region. Results here can serve as a precursor to other studies in order to estimate the global burden. A collaboration of diabetes experts from these articles can also raise awareness of the severity of this issue. More importantly, the public health implications of communicating these findings to influential policy makers can have a profound effect on health-related earmarked funding and future program development.

These pooled diabetes prevalence results suggest that populations of high-income countries should be targeted for preventive intervention strategies tailored toward rural groups.

We should extend diabetes prevention programs from urban to rural settings in high-income countries and collaborate globally to reduce diabetes disability and improve overall quality of life. As we approach the year 2030, where projections estimate that one in every ten persons will have developed diabetes, we will continue to experience an even more unmanageable problem unless proactive steps are taken to reduce our current global diabetes burden.

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APPENDIX

Figure 1: Search Strategy

EMBASE, MEDLINE via Pubmed, CINAHL, and Cochrane Databases (from January 1990 until January 2012)
#1 "diabetes" #2 "prevalence" #3 "epidemiology" #4 "morbidity" #5 OR/ 2-4 #6 "rural" #7 Andorra OR Aruba OR Australia OR Austria OR Bahamas OR Bahrain OR Barbados OR Belgium OR Bermuda OR Brunei Darussalam OR Canada OR Cayman Islands OR Channel Islands OR Hong Kong OR Macao OR Croatia OR Curacao OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Equatorial Guinea OR Faeroe Islands OR Finland OR France OR French Polynesia OR Germany OR Gibraltar OR Greece OR Greenland OR Guam OR Hungary OR Iceland OR Ireland OR Isle of Man OR Israel OR Italy OR Japan OR Korea OR Kuwait OR Liechtenstein OR Luxembourg OR Malta OR Monaco OR Netherlands OR New Caledonia OR New Zealand OR Northern Mariana Islands OR Norway OR Oman OR Poland OR Portugal OR Puerto Rico OR Qatar OR San Marino OR Saudi Arabia OR Singapore OR Sint Maarten OR Slovak Republic OR Slovenia OR Spain OR (Saint Martin OR St. Martin) OR Sweden OR Switzerland OR (Trinidad and Tobago) OR (Turks and Caicos Islands) OR United Arab Emirates OR United Kingdom OR England OR Northern Ireland OR Scotland OR Wales OR Great Britain OR United States OR Virgin Islands #8 1 AND 5 AND 6 AND 7

Table 1: Countries with High-Income Economies

Andorra	French Polynesia	Norway
Aruba	Germany	Oman
Australia	Gibraltar	Poland
Austria	Great Britain	Portugal
Bahamas, The	Greece	Puerto Rico
Bahrain	Greenland	Qatar
Barbados	Guam	San Marino
Belgium	Hungary	Saudi Arabia
Bermuda	Iceland	Scotland
Brunei Darussalam	Ireland	Singapore
Canada	Isle of Man	Sint Maarten
Cayman Islands	Israel	Slovak Republic
Channel Islands	Italy	Slovenia
Hong Kong and Macao (of China)	Japan	Spain
Croatia	Korea, Republic of	St. Martin
Curacao	Kuwait	Sweden
Cyprus	Liechtenstein	Switzerland
Czech Republic	Luxembourg	Trinidad and Tobago
Denmark	Malta	Turks and Caicos Islands
England	Monaco	United Arab Emirates
Estonia	Netherlands	United Kingdom
Equatorial Guinea	New Caledonia	United States
Faeroe Islands	New Zealand	Virgin Islands (U.S.)
Finland	Northern Ireland	Wales
France	Northern Mariana Islands	

*High-income economies are defined by the World Bank as those with a GDP per capita of $12,276 or more (21).

Figure 2: Selection strategy for included articles

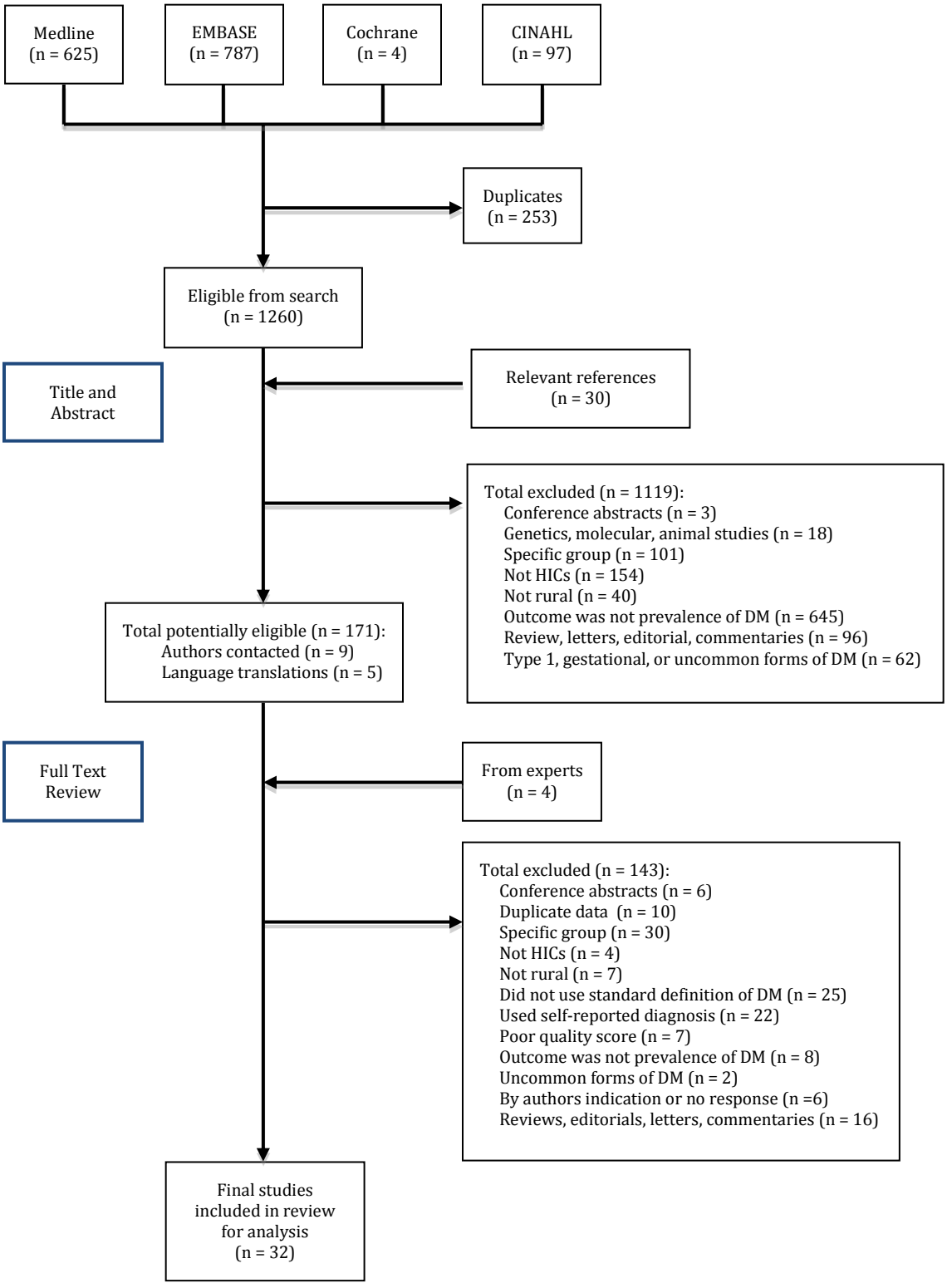


Table 2: Values for diagnosis of diabetes mellitus by WHO and ADA

	Glucose Concentration, mmol/L (md/dL)		
	Whole Blood		Plasma
	Venous	**Capillary**	**Venous**
Diabetes Mellitus (WHO 1999)			
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
2-h post-glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
or both			
Diabetes Mellitus (ADA 2003)			
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
2-h post-glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
or both			
Diabetes Mellitus (ADA 1997)			
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
2-h post-glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
or both			
Diabetes Mellitus (WHO 1985)			
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.8 (≥ 140)
2-h post-glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
or both			

Table 3: WHO Regions and Designated Countries

Africa	The Americas	Southeast Asia	Europe	Eastern Mediterranean	Western Pacific
Algeria	Antigua and Barbuda	Bangladesh	Albania	Afghanistan	Australia
Benin	Argentina	Bhutan	Andorra	Bahrain	Brunei Darussalam
Botswana	Bahamas	Democratic People's Republic of Korea	Armenia	Djibouti	Cambodia
Burkina Faso	Barbados	India	Austria	Egypt	China
Burundi	Belize	Indonesia	Azerbaijan	Iran	Cook Islands
Cameroon	Bolivia	Maldives	Belarus	Iraq	Fiji
Central African Republic	Brazil	Myanmar	Belgium	Jordan	Japan
Chad	Canada	Nepal	Bosnia and Herzegovina	Kuwait	Kiribati
Comoros	Chile	Sri Lanka	Bulgaria	Lebanon	Lao People's Democratic Republic
Congo	Colombia	Thailand	Croatia	Libya	Malaysia
Cote d'Ivoire	Costa Rica	Timor-Leste	Cyprus	Morocco	Marshall Islands
Democratic Republic of the Congo	Cuba		Czech Republic	Oman	Micronesia
Equatorial Guinea	Dominica		Denmark	Pakistan	Mongolia
Eritrea	Dominican Republic		Estonia	Qatar	Nauru
Ethiopia	Ecuador		Finland	Saudi Arabia	New Zealand
Gabon	El Salvador		France	Somalia	Niue
Gambia	Grenada		Georgia	South Sudan	Palau
Ghana	Guatemala		Germany	Sudan	Papua New Guinea
Guinea	Guyana		Greece	Syrian Arab Republic	Philippines
Guinea-Bissau	Haiti		Hungary	Tunisia	Republic of Korea
Kenya	Honduras		Iceland	United Arab Emirates	Samoa
Lesotho	Jamaica		Ireland	Yemen	Singapore
Liberia	Mexico		Israel		Solomon Islands
Madagascar	Nicaragua		Italy		Tonga
Malawi	Panama		Kazakhstan		Tuvalu
Mali	Paraguay		Kyrgyzstan		Vanuatu
Mauritius	Peru		Latvia		Vietnam
Mozambique	Saint Kitts and		Lithuania		

	Nevis				
Namibia	Saint Lucia		Luxembourg		
Niger	Saint Vincent and the Grenadines		Malta		
Nigeria	Suriname		Monaco		
Rwanda	Trinidad and Tobago		Montenegro		
Sao Tome and Principe	United States of America		Netherlands		
Senegal	Uruguay		Norway		
Seychelles	Venezuela		Poland		
Sierra Leone			Portugal		
South Africa			Moldova		
Swaziland			Romania		
Togo			Russian Federation		
Uganda			San Marino		
Tanzania			Serbia		
Zambia			Slovakia		
Zimbabwe			Slovenia		
			Spain		
			Sweden		
			Switzerland		
			Tajikistan		
			Yugoslav Republic of Macedonia		
			Turkey		
			Turkmenistan		
			Ukraine		
			United Kingdom		
			Uzbekistan		

Figure 3: Rural diabetes pooled prevalence of high-income countries by geographic region

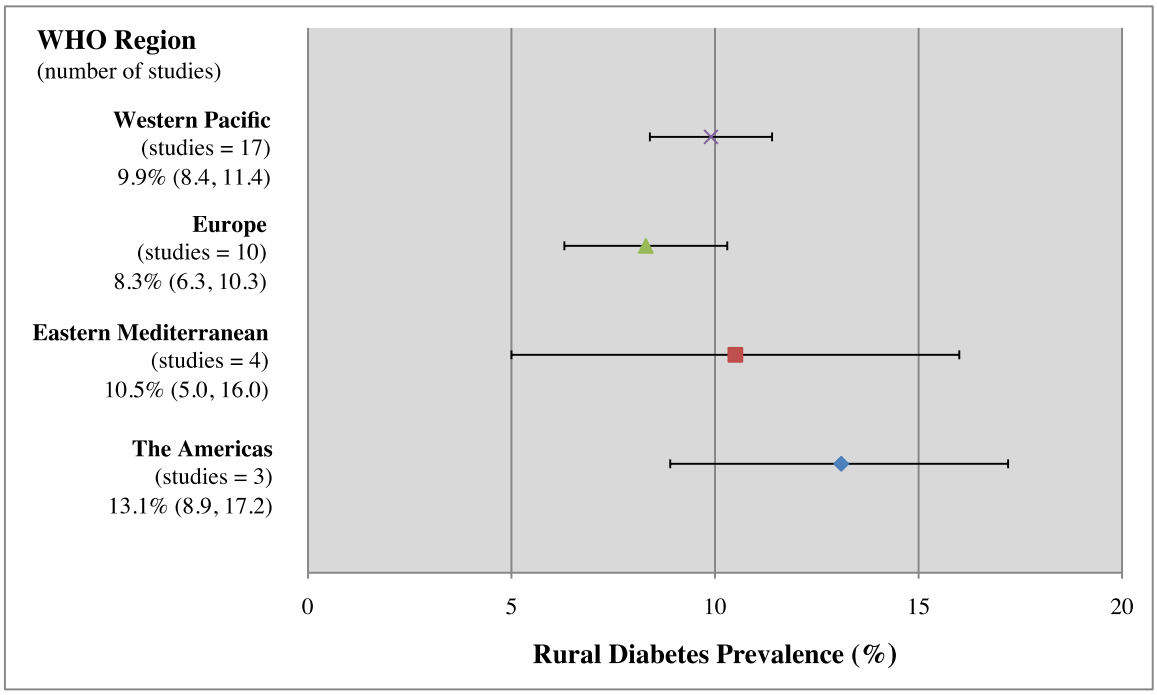
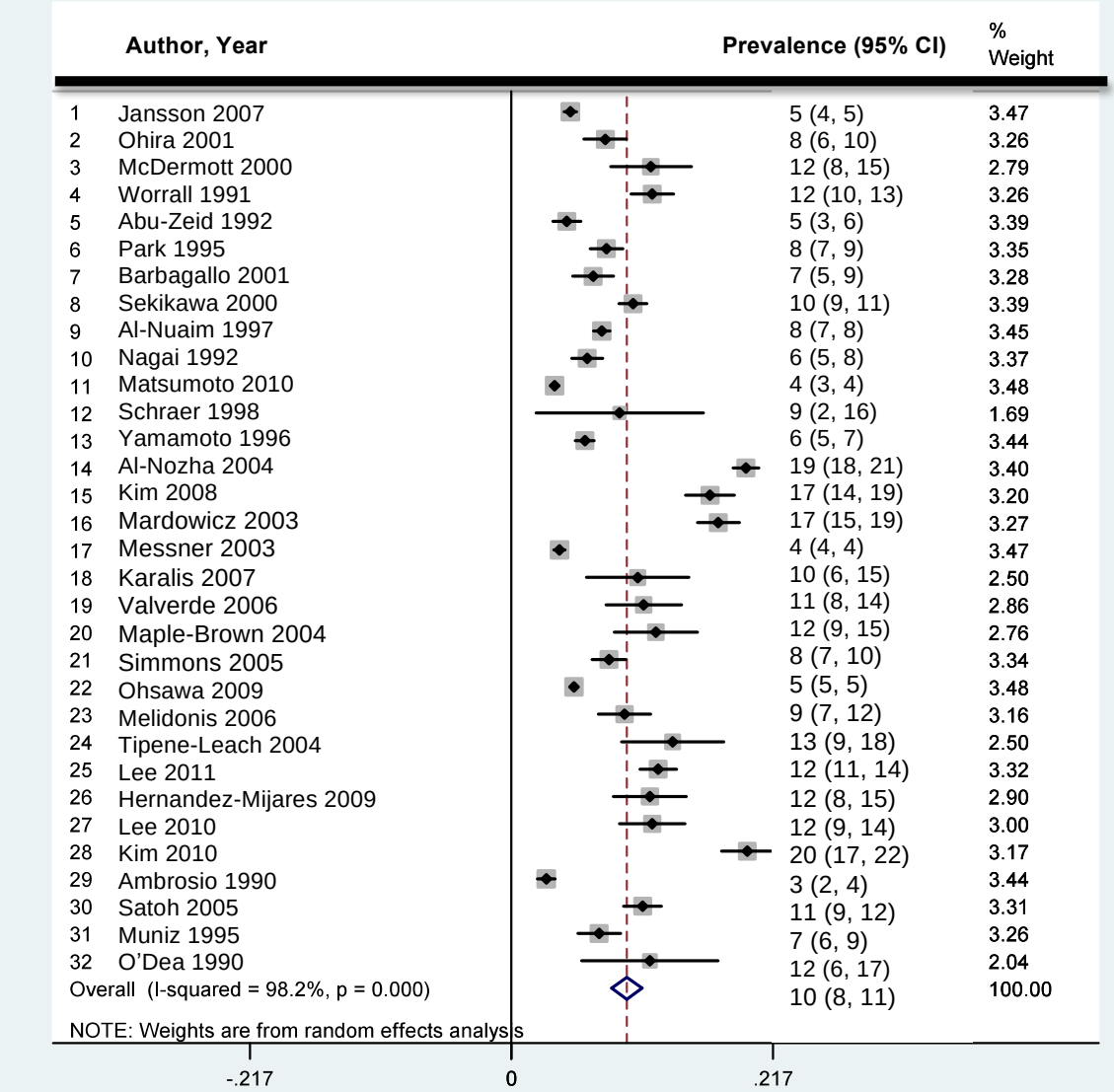


Table 4: Rural diabetes pooled prevalence estimates by country

Country	Studies (34 studies)	Prevalence (%, 95% CI)	Heterogeneity (I^2, %)	p-value
The Americas	3	13.1 (8.9, 17.2)	85.5	0.001
Canada	1	11.7 (9.9, 13.5)	--	--
USA	2	13.5 (6.3, 20.7)	75.7	0.043
Eastern Mediterranean	3	10.5 (2.4, 18.7)	98.2	<0.001
Saudi Arabia	3	10.5 (2.4, 18.7)	99.5	<0.001
Europe	10	8.3 (6.3, 10.3)	97.0	<0.001
Greece	2	9.6 (7.7, 11.6)	00.0	0.650
Italy	2	4.8 (1.0, 8.6)	94.0	0.007
Poland	1	17.2 (15.5, 18.9)	--	--
Spain	3	9.7 (6.7, 12.7)	74.1	0.021
Sweden	2	4.4 (3.6, 5.3)	84.4	0.000
Western Pacific	16	9.5 (8.1, 11.0)	97.1	<0.001
Australia	4	10.3 (7.9, 12.8)	59.8	0.059
Japan	7	7.0 (5.6, 8.5)	97.3	0.001
Korea	4	12.8 (8.0, 17.6)	96.4	0.002
New Zealand	1	13.4 (9.2, 17.6)	--	--

*Note: Homogeneity confirmed within studies for Greece, where $I^2 = 0$; no inconsistencies found in the effect size except due to sampling error within the studies

Figure 4: Pooled prevalence of diabetes among rural areas of high-income countries by study author, 1990- 2011



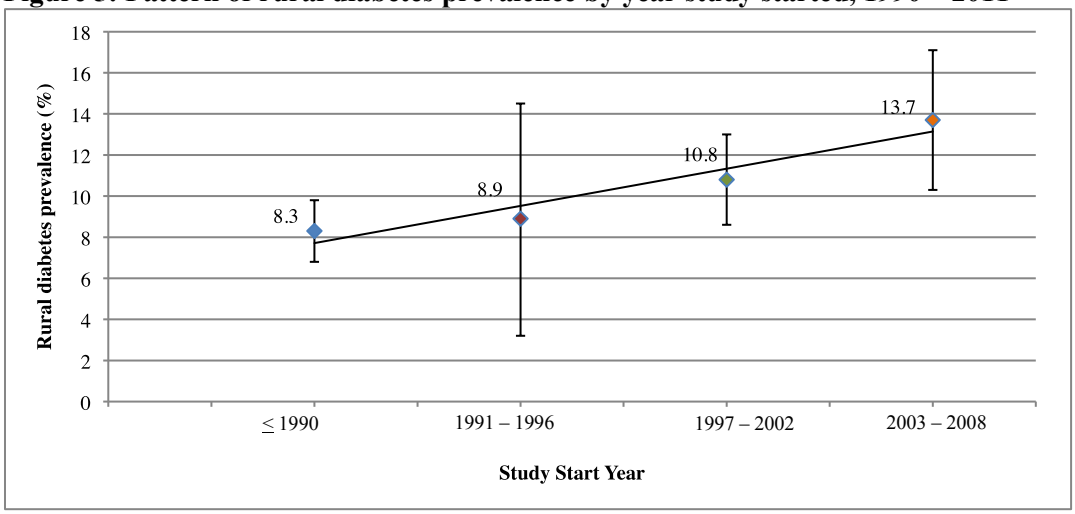
*Studies are arranged in alphabetical order by author name (32 studies). The blue diamond indicates the pooled prevalence of rural diabetes for studies listed. Black diamonds indicate the prevalence for each study; the length of the grey rectangles a representative of the weight for each study. The horizontal lines are the 95% confidence intervals. The red-dashed line intersecting the unfilled blue diamond is to show how each study compares to the pooled prevalence estimate.

Table 5: Rural diabetes pooled prevalence estimates by year study started and country

	Countries Represented in Analysis by 6-Year Interval			
	≤1990 n = 19,696	1991 – 1996 n = 22,599	1997 – 2002 n = 39,504	2003 – 2008 n = 4,316
	Japan (2) Canada (1) Korea (1) Australia (1) Sweden (1) Saudi Arabia (2) Italy (1)	Japan (3) USA (1)	Japan (1) USA (1) Poland (1) Australia (2) Sweden (1) Spain (1) Greece (2)	New Zealand (1) Spain (1) Korea (3)
Period Prevalence (%, 95% CI)	8 studies* 8.3 (6.8, 9.8)	5 studies* 8.9 (3.2, 14.5)	9 studies 10.8 (8.6, 13.0)	5 studies 13.7 (10.3, 17.1)

*5 studies missing because no information on study start year

Figure 5: Pattern of rural diabetes prevalence by year study started, 1990 – 2011

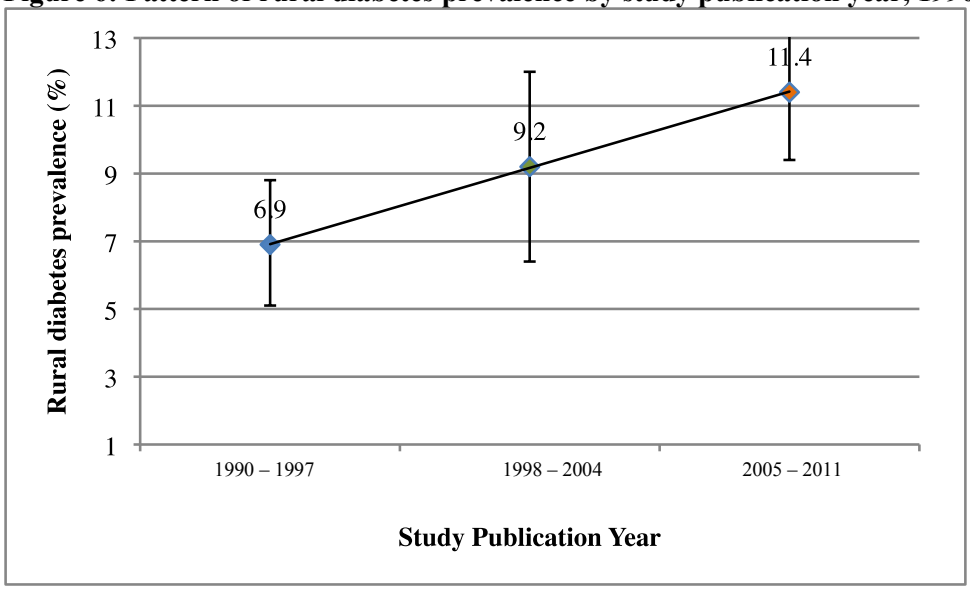


* Blue = Japan, Canada, Korea, Australia, Sweden, Saudi Arabia, Italy
Red = Japan, USA
Green = Japan, USA, Australia, Sweden, Greece, Poland, Spain
Orange = New Zealand, Spain, Korea

Table 6: Rural diabetes pooled prevalence estimates by publication year and country

	Countries Represented in Analysis by 7-Year Interval		
	1990 – 1997 n = 17,549	1998 – 2004 n = 19,296	2005 – 2011 n = 54,850
	Japan (2) Korea (1) Canada (1) Australia (1) Saudi Arabia (2) Italy (1) Spain (1)	Japan (2) Poland (1) USA (1) Australia (2) Saudi Arabia (1) Italy (1) Sweden (1) New Zealand (1)	Japan (3) Korea (3) USA (1) Australia (1) Spain (2) Greece (2) Sweden (1)
Period Prevalence (%, 95% CI)	9 studies 6.9 (5.1, 8.8)	10 studies 9.2 (6.4, 12.0)	13 studies 11.4 (9.1, 13.2)

Figure 6: Pattern of rural diabetes prevalence by study publication year, 1990 – 2011



* Blue = Japan, Canada, Korea, Australia, Saudi Arabia, Italy, Spain
Green = Japan, USA, Korea, Australia, Saudi Arabia, Poland, New Zealand, Italy, Sweden
Orange = Japan, USA, Korea, Australia, Greece, Sweden, Spain

Table 7: Meta-Regression Analysis Investigating Factors Influencing Pooled Diabetes Prevalence Across Rural Areas of High-Income Countries, 1990 – 2011

	All Studies (32)	
	Coefficient	95% CI*
Publication year	0.26	(-0.02, 0.54)
Proportion of participants who were male	-0.03	(-0.41, 0.35)
Studies with national representative samples	-0.32	(-9.51, 8.86)

*CI = Confidence Interval

EMORY UNIVERSITY

Institutional Review Board

28 February, 2012

Isabelle Sanchez
Emory University
School of Public Health: Thesis
Atlanta, GA

RE: Determination: No IRB Review Required
56640- Title: *The Prevalence of Diabetes in Rural Areas of High-Income Countries: A Systematic Review and Meta-Analysis*
PI: Isabelle Sanchez

Dear Ms. Sanchez,

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of research involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will be conducting a secondary review of published literature.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Julia Duckworth, MS
Research Protocol Analyst
Emory University Institutional Review Board
1599 Clifton Road
Atlanta, GA 30322
Office: 404-727-3401
Fax: 404-727-1358
e-mail: Julia.isabella.duckworth@emory.edu

This letter has been electronically signed.

Table 8: Characteristics of Included Studies

Author, year of publication	Country	Study Period	DM type	Diagnostic method[1]	Validated DM Criteria	Age range	Mean age	Male (%)	Description of rural area used	Design	Sample Frame	Sample Method	Quality[2]
Worrall, 1991[50]	Canada	1989 – 1990	1, 2	FPG (capillary)	WHO 1985	≥ 40			Clinics in Gander, rural Newfoundland	Cohort	Census 1986	Random	2,3
Kim, 2008[35]	USA	1997 – 2000	2	OGT (venous)	WHO 1999	18 – 95	49.2	45.8	North Kohala, Hawaii	Cross-sectional	Kahala Health Project	Total population invitation	2,3
Schraer, 1998[45]	USA	1992	2	OGT	WHO 1985	≥ 40	59	45	Remote Yupik Eskimo village, St. Lawrence Island, Alaska	Cross-sectional	Subset of Strong Heart Study for CVD	Total population invitation	3,4
Abu-Zeid, 1992[14]	Saudi Arabia	1989	1, 2	FPG (capillary), previous physician diagnosis	WHO 1985	≥ 10		50.6	Al-Malaha villages 12 km north of Abha	Cross-sectional	Local health center areas	Total population invitation	2,3,4
Al-Nozha, 2004[6]	Saudi Arabia	1995 – 2000	1, 2	FPG (venous)	ADA 2003	30 – 70			Total number of health centers in community	Cohort	Local health center areas	Stratified cluster	1,2,3,4
Al-Nuaim, 1997[12]	Saudi Arabia	1990 – 1993	1, 2	FPG, OGT (venous)	WHO 1985	≥ 15		51.4	Agricultural villages from different regions	Cohort	National Epi Survey for Metabolic Diseases	Multi-stage stratified cluster random	1,2,3,4
Karalis, 2007[34]	Greece	2000 – 2002	1, 2	FPG, RBG and diabetes symptoms, previous physician diagnosis	ADA 1997		62.4	46	Village of Spilli, Crete	Cross-sectional	Unspecified	Total population invitation	2,3
Melidonis, 2006[9]	Greece	2002	1, 2	FPG (venous), hypoglycemic medication	WHO 1999	21 – 99	47.5	44.6	Agricultural villages	Cross-sectional	Census 2010	Total population invitation	3,4
Ambrosio, 1990[32]	Italy		1, 2	FPG, previous physician diagnosis	WHO 1999	20 – 59		50.1	Veneto region, a semi-rural population of Mirano, Venice	Cross-sectional	Italian National Research Council	Stratified random sample of 10% residents	2,3,4
Barbagallo, 2001[94]	Italy	1989 – 1997	1, 2	FPG, hypoglycemic medication	WHO 1985	20 – 69	46.6	43.5	Ventimiglia di Sicilia	Cross-sectional	Ventimigla di Sicilia Projects	Total population invitation	3,4
Mardarowicz, 2003[39]	Poland	1998 – 2001	2	FPG, OGT (venous)	WHO 1985	≥ 35		44	communes in the countryside of Lubelskie Voivodship province in Lublin region, Eastern	Cross-sectional	Unspecified	Total population invitation	2,3,4
Hernandez-Mijares, 2009[33]	Spain	2005 – 2006	1, 2	FPG, OGT (venous)	ADA 2003	≥ 18			Areas <10,000 inhabitants of Castellon, East Spain	Cross-sectional	Census 2008	Multi-stage stratified random	2,3,4
Muniz, 1995[10]	Spain		1, 2	FPG (capillary), previous physician diagnosis	WHO 1985	40 – 69		46.8	Areas <50,000 inhabitants in the community of Galicia	Cross-sectional	Census	Multi-stage stratified random	2,3,4
Valverde, 2006[15]	Spain	2001	1, 2	FPG	ADA 1997	≥ 20		49.2	Areas <2,000 inhabitants in the Murcia region SW	Cross-sectional	Unspecified	Multi-stage stratified random	3,4
Jansson, 2007[7]	Sweden	1972 – 2001	2	FPG, OGT (capillary)	WHO 1999	35 – 79		50.7	Laxa, a small municipality in Orebro county, central Sweden	Cohort	Laxa Diabetes Registry from health center	Total population invitation	2,3,4
Messner, 2003[8]	Sweden	1999	1, 2	FPG, OGT (venous), hypoglycemic medication	WHO 1985	25 – 64	45.6		Subarctic areas of <15,000 inhabitants in North Sweden	Cohort	MONICA Northern Sweden	Random	3,4
Maple-Brown, 2004[38]	Australia	2001 – 2002	2	FPG (venous), previous physician diagnosis	WHO 1999	≥ 15	50	40	Northeast Arnhemland, Northern Territory	Cross-sectional	Census	Total population invitation	2,3
McDermott, 2000[40]	Australia	1987 – 1990	1, 2	FPG, OGT (venous)	WHO 1985	≥ 15		46.3	Aboriginal community in Central Australia	Cross-sectional	Census	Total population invitation	2,3

Author, year of publication	Country	Study Period	DM type	Diagnostic method[1]	Validated DM Criteria	Age range	Mean age	Male (%)	Description of rural area used	Design	Sample Frame	Sample Method	Quality[2]
O'Dea, 1990[41]	Australia		1, 2	FPG, OGT (venous)	WHO 1985	≥ 17	35.5	41	Small community south of Darwin in northwest of the Northern Territory	Cross-sectional	Unspecified	Total population invitation	2,3,4
Simmons, 2005[47]	Australia	2001 – 2003	1, 2	OGT (venous)	WHO 1999	≥ 25		43.7	Shepparton-Mooroopna and surrounding capitals in Goulburn Valley, rural Victoria	Cross-sectional	Census 2001, Crossroads Undiagnosed Disease Study	Stratified random cluster	3,4
Matsumoto, 2010[27]	Japan	1992 – 1995	1, 2	FPG, OGT, hypoglycemic medication	ADA 2003	30 – 69	55.3	39.2	Rural municipalities of Iwaizumi, Tako, Yamato, Kuze, Takasu, Wara, Sakuma, Hokudan, Sakugi, Ohkawa, Shingu, and Akaike in Japan	Cohort	Census from the Whole Nation Municipality-level Area Data	Unspecified	3,4
Nagai, 1992[52]	Japan	1991	1, 2	FPG, OGT	WHO 1985	≥ 35		40.3	Ojika island, Ojika-cho town, Kitamatsuura-gun (North Matsuura county), Nagasaki prefecture; 3 hour ferry ride from the port city of Sasebo, Saga prefecture on main island of Kyushu	Cross-sectional	Ojika island resident registration data	Total population invitation	3,4
Ohira, 2001[42]	Japan	1985	1, 2	FPG, OGT, hypoglycemic medication	WHO 1985	40 – 78	59	35.4	rural community of Kyowa, Ibaraki perfecture	Cohort	Unspecified	Total population invitation	2,3
Ohsawa, 2009[26]	Japan	2002 – 2004	1, 2	FPG (venous), A1C, hypoglycemic medication	ADA 2003	≥ 18		34.6	Tohoku area, a rual part of northeastern mainland of Japan	Cohort	Unspecified	Multi-stage stratified	2,3,4
Satoh, 2005[44]	Japan		1, 2	FPG (venous), A1C, hypoglycemic medication	ADA 2003	≥ 40	62.3	48.2	farming community of Tanushimaru town in southwestern Japan	Cross-sectional	Unspecified	Total population invitation	2,3,4
Sekikawa, 2000[46]	Japan	1990 – 1992	2	OGT	WHO 1985	≥ 40		44	No hospitals in the area; Funagata town, Yamagata perfecture on Honshu Island, Japan	Cross-sectional	Unspecified	Total population invitation	2,3,4
Yamamoto, 1996[51]	Japan	1992 – 1994	1, 2	FPG, OGT (venous)	WHO 1985	≥ 20	56.7	34.3	Yamatomachi, Niigata Perfecture	Cross-sectional	Unspecified	Total population invitation	2,3,4
Kim, 2010[36]	Korea	2007 – 2008	1, 2	FPG	WHO 1999	≥ 40	65.8	38.1	rural area of Chungju City, Korea	Cross-sectional	Unspecified	Stratified random cluster	3,4
Lee, 2011[37]	Korea	2003	1, 2	FPG, OGT (venous)	ADA 2003	≥ 20		38.4	rural district of Dalseong-gun in Daegu City, Korea	Cross-sectional	Unspecified	Multi-stage cluster	3,4
Lee, 2010[5]	Korea	2005	2	FPG, OGT (venous)	ADA 2003	≥ 30	60	40.6	Haman-gun community in Gyeongsangnam-do	Cross-sectional	Unspecified	Stratified random cluster	3,4
Park, 1995[43]	Korea	1989 – 1991	1, 2	OGT	WHO 1985	30 - 64			population <5,000 people/km^2; rural neighborhoods in Yonchon County, located in northern Kyunggi Province	Cross-sectional	1991 household registration records	Random cluster	2,3,4
Tipene-Leach, 2007[49]	New Zealand	2003	2	OGT	WHO 1999	≥ 25	49.3	38.1	Ngati Porou Hauora along rural East Coast area, north of Gisborne, in the North Island	Cross-sectional	Registered survey in East & Gisborne	Multi-stage stratified random	3,4

[1] FPG= fasting plasma glucose, OGT= oral glucose tolerance test

[2] Quality scores: 1= study national representativeness, 2= no non-response bias, 3= objective methods used, 4= use of appropriate statistical method