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The risk of mortality among people with type 2 diabetes mellitus in Latin America: A systematic review and meta-analysis of population-based cohort studies

Diabetes mortality in Latin America

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ABSTRACT

Type 2 Diabetes mellitus (T2DM) is associated with a high mortality risk, though the magnitude of this association remains unknown in Latin America (LA). We aimed to assess the strength of the association between T2DM and all-cause and cause-specific mortality in population-based cohort studies in LA. Systematic review and meta-analysis. The inclusion criteria were: i) men and women ≥ 18 years-old with T2DM; ii) study outcomes all-cause and/or cause-specific mortality; and iii) using people without T2DM as comparison group. Five databases (Scopus, Medline, Embase, Global Health and LILACS) were searched. Risk of bias was evaluated with the Robins-I criteria. Initially there were 979 identified studies, of which seventeen were selected for qualitative synthesis; 14 were included in the meta-analysis (N=416,821). Self-reported T2DM showed a pooled relative risk (RR) of 2.49 for all-causes mortality (I-squared [I^2]=85.7%, $p < 0.001$; 95% confidence interval [CI] 1.96-3.15). T2DM based on a composite definition was associated with a 2.26-fold higher all-cause mortality ($I^2=93.9\%$, $p < 0.001$; 95% CI: 1.36-3.74). The pooled risk estimates were similar between men and women, though higher at younger ages. The pooled RR for cardiovascular mortality was 2.76 ($I^2=59.2\%$; $p < 0.061$; 95% CI: 1.99-3.82), and for renal mortality 15.85 ($I^2=0.00\%$; $p < 0.645$; 95% CI: 9.82-25.57). Using available population-based cohort studies this work has identified and estimated the strength of the association between T2DM and mortality in LA. The higher mortality risk compared with high-income countries deserves close attention from health policies makers and clinicians to improve diabetes care and control hence preventing complications and delaying death.

Key words: Diabetes; mortality; cohort studies; Latin America

INTRODUCTION

The International Diabetes Federation (IDF) has recently alerted that the number of adults with diabetes is expected to rise worldwide from 325 million in 2017 to 629 million by 2045.¹ There is convincing scientific evidence that type 2 diabetes mellitus (T2DM) is associated with negative effects on morbidity, increased mortality, disability and a decrease in quality of life.²⁻⁷ Moreover, T2DM imposes a heavy economic burden on health-care systems.⁸ One of the main challenges of clinical medicine and public health is to decrease mortality due to T2DM. Most studies on the association between T2DM and mortality have been conducted in high-income countries. Studies in regions such as Latin America (LA) are scant.

LA includes mainly low- and middle-income countries and presents an heterogeneous profile of non-communicable diseases and risk factors for non-communicable diseases, whereby some countries have higher prevalence of certain risk factors (e.g., high diabetes prevalence) though others remain low or have decreased over time;⁹⁻¹¹ in addition, access to health-care systems differs between and within countries in LA.¹² The synergism among these parameters, and their divergence in comparison to those of other world regions, may lead to different T2DM mortality. For health-policy makers, public health professionals and the health-care systems of LA, it may be useful to understand the differences of T2DM-related mortality between the continents and regions. This will help to identify research gaps and provide evidence as well as guidance for public health policies and clinical practice in the region.

Due to the lack of available scientific data on the associations of T2DM and mortality in LA, we conducted a systematic review and meta-analysis to assess the strength of the association between T2DM and all-cause and cause-specific mortality in LA.

METHODS

Protocol

This is a systematic review of the literature with meta-analysis of data summary. The methods and reporting follow the PRISMA statement.¹³ The protocol was registered at PROSPERO (CRD42018115406).

Eligibility criteria

The inclusion criteria of the population-based prospective cohort studies in LA were i) adult men and women diagnosed with T2DM; ii) study outcomes all-cause and/or cause-specific mortality; and; iii) using people without T2DM as comparison group.

Information sources

The search was conducted from database inception to October 30th, 2018 in Scopus, Medline, Embase, Global Health (the last three through Ovid), and LILACS, a LA-based search engine. The search terms used are presented in Supplementary Material p. 02. No other sources of information were systematically sought, though two additional references (conference abstracts) known by the authors were included. Moreover, the authors accessed unpublished results of a prospective population-based cohort in Peru.^{14,15}

Study selection

Results from the search were downloaded and saved in EndNote where duplicates were removed. A second check for duplicates was conducted using Rayyan, an online software that was also used during the study selection process.¹⁶ Two reviewers (RMC-L and AB-O) independently reviewed titles and abstracts. Disagreements were solved by consensus between them. Likewise, these two reviewers independently studied the full-text manuscript of the selected studies and solved any disagreements by consensus.

Risk of bias

Risk of bias was assessed by one reviewer (LA-F) and independently verified by another one (AB-O); discrepancies were solved by consensus between them. The risk of bias of each selected study was evaluated following the ROBINS-I criteria.¹⁷

Data collection

Before any data was collected, two reviewers (RMC-L and AB-O) agreed on the information that needed to be extracted to address the research question. These items were summarized in an Excel spreadsheet and were not modified during data collation. The information collected included study setting, study design, year of baseline examination, sample size, demographical characteristics at baseline (e.g., sex and age), follow-up time, and definition of T2DM used in the report. Similarly, risk estimates for the association between T2DM and mortality were recorded. The study outcomes included all-cause, cardiovascular disease and renal mortality. According to data availability, either overall estimates (including all ages and both genders) or sex- and age-stratified estimates, were registered. The obtained information included either relative risks (RR) or hazard ratios (HR) along with their corresponding 95% confidence intervals (95% CI).

Synthesis of results

The results were summarized using qualitative and quantitative methods. Key characteristics of the selected studies were summarized and presented qualitatively in tables and text. For the quantitative data, three steps were applied. First, the risk estimates extracted from the reports were log transformed (transformation from the exponential form to their log form). Second, the standard errors were computed from the 95% CIs. For this, each CI was first log transformed. The standard error was estimated following the regular methods.¹⁸ Third, a random-effects meta-analysis was conducted following the DerSimonian & Laird method using the *randomi* option in STATA 13.0 (StataCorp, College Station, TX, US). A random-effect approach was applied because of the heterogeneity across study populations and years of data collection.

The risk estimates included in this meta-analysis were those of the fully adjusted models. The pooled risks were estimated for all-cause, cardiovascular disease and renal mortality for men and women separately and combined. In addition, all risk estimates were calculated according to age groups as well. When only age-stratified risk estimates were reported, a random-effect meta-analysis was first conducted using these estimates to compute the overall risk estimate for each given study.¹⁹ In case that only sex-stratified estimates were available, these were meta-analysed independently to compute the overall risk estimate.²⁰ Likewise, when different age groups were used, these were combined and meta-analysed independently so that these age bands would resemble those of the other studies. This approach was applied for a report that presented results in the following groups: 35-49, 50-59,

60-69 and 70-74;²¹ the first two and the last two groups were combined and meta-analysed. Therefore, the new age groups were more like those reported by two of the other studies identified (30-59, 60-74 and 74-84years-of-age).^{19,22}

Publication bias was assessed using Funnel plots for each outcome of interest. Additional statistical tests were not conducted because these have low efficacy when fewer than ten studies are meta-analysed, which was the case for all the outcomes herein assessed. Most of the studies reported HR. Two studies that reported RR were pooled along the HR because their methodologies were equivalent to reporting HR.^{19,21} However, two studies were excluded from the quantitative analysis because one reported RR following a different analytical approach and the other estimated odds ratios instead.^{23,24} The results of the meta-analysis are presented as RR (95% CI).

Ethical statement

This is a systematic review and meta-analysis of published and open information. No human subjects were involved in this project. Thus, this study was classified as non-human subject research.

Therefore, no approval was needed from an IRB committee.

RESULTS

Study selection

The literature search yielded 976 results. In addition, three studies were added from additional sources (two conference abstracts and one unpublished results). After duplicates were excluded, 828 titles and abstracts were reviewed, 801 of these were excluded and, hence, 27 scientific papers were studied in detail (Supplementary Material p. 03). Seventeen papers were included for the qualitative synthesis (including one unpublished work).¹⁹⁻³⁴ Of these seventeen studies, three were excluded from the meta-analyses: two publications reported on the same study,^{19,33} i.e., only included once in the quantitative synthesis; and two studies were excluded because the risk estimates were computed differently (see methods section);^{23,24} Therefore, fourteen reports were included for the final quantitative synthesis (N=416,821).^{19-22,25-32,34}

Study characteristics

Table 1 presents the characteristics of the selected seventeen reports. The oldest studies started in 1976-78,²⁷ three in the 1980s,^{20,24,25} five in the 1990s,^{19,22,26,28,31,33} and six in the 2000s.^{23,29,30,32,34} It was not possible to retrieve this information from two publications.^{21,35} Eleven studies based their estimates on self-reported T2DM diagnosis,^{19-23,25,27,28,30,33,34} while six used a composite definition (e.g., self-reported and fasting glucose).^{24,26,29,31,32,35}

Risk of bias within studies

All the selected studies were of moderate quality, mainly because attrition rates were not appropriately reported; none showed a high risk of bias in any domain. A detailed risk of bias assessment for each study is shown in Supplementary Material pp. 04-06.

Mortality risk

Across the outcomes of interest, sex and age groups, all studies revealed a positive association between T2DM and mortality.^{19-22,25-32,34,35}

For all-cause mortality, nine studies were analysed using self-reported diabetes as the exposure.^{19-22,25,27,28,30,34} These studies showed an increased mortality risk in patients with T2DM compared with

people without T2DM. The RR ranged from 1.47 (95% CI: 1.18-1.84)³⁰ to 6.64 (95% CI: 1.94-22.79).²⁸

The meta-analysis of these reports suggested that T2DM was associated with a 2.49-fold higher all-cause mortality risk (I-squared 85.7%, Figure 1A). On the other hand, the meta-analysis of the five

studies that used a composite definition of T2DM revealed RRs from 1.47 (95% CI: 1.31-1.65)³¹ to 4.38 (95% CI: 3.43-5.59).²⁶ The meta-analysis of these five reports indicated that T2DM was associated with a 2.26-fold risk of all-cause mortality (I-squared 93.9%, Figure 1B).

Regarding cardiovascular mortality, four studies using self-reported diagnosis were included in the meta-analysis.^{19,25,27,34} The individual RR estimates varied between 1.50 (95% CI: 0.85-2.65)²⁵ and 3.78 (95% CI: 2.52-5.67).³⁴ The pooled estimate showed that T2DM was associated with a 2.76-fold increased risk of cardiovascular mortality (I-squared 59.2%, Figure 2). Likewise, renal mortality was used as an endpoint in two reports (I-squared 00.0%, Figure 3),^{19,34} revealing a pooled RR estimate of 15.85 (95% CI: 9.82-25.57).

T2DM related mortality by gender and age

All-cause mortality according to sex was presented in two reports.^{20,30} The pooled RR estimate (Figure 4A and 4B) for men was 1.95 (95% CI: 1.16-3.26) and for women 1.98 (95% CI: 0.95-4.10). All-cause mortality by age groups was assessed in three studies.^{19,21,22} In general, they showed reduced risk estimates with increasing age. The pooled RR for the age group 35-59 years-old (I-squared 97.2%, Figure 5A) was 3.15 (95% CI: 1.74-5.70). The corresponding RR for those aged 60 to 74 years (I-squared 96.0%, Figure 5B) was 2.37 (95% CI: 1.76-3.17). It was not possible to calculate sex- or age-specific risk estimates for cardiovascular or renal deaths due to the lack of data available.

Risk of bias across studies

Funnel plots for all the outcomes above detailed are available in Supplementary Material pp. 07-10. These plots revealed some publication bias. However, they should be interpreted cautiously because there were only a few studies available for some specific outcomes such as cardiovascular or renal mortality.

Other causes of death

A study conducted in Mexico using self-reported T2DM as exposure variable studied several other causes of death as main outcome.^{19,33} They found a higher risk of mortality due to infectious diseases across all age groups (35-59 years-old [RR=8.6 (95% CI: 6.5-11.4)], 60-74years-old [RR=3.8 (95% CI: 3.1-4.2)] and 75-84 years-old [RR=2.5 (95% CI: 2.0-3.1)]).¹⁹ Notwithstanding, they found less conclusive evidence for other causes such as peptic ulcer (not significant at the oldest age group) and neoplasms (not significant across age groups).¹⁹

DISCUSSION

Summary of evidence

This is the first meta-analysis conducted estimating the mortality risk among people with T2DM in population-based cohorts of patients with self-reported T2DM or a composite definition of T2DM (self-reported plus biomarkers) in LA. Furthermore, our study calculated the pooled mortality risk for cardiovascular and renal mortality. Our results revealed that the pooled all-cause mortality among people with T2DM is more than two-times higher in comparison with people without T2DM. Moreover, this risk being higher when the diagnosis of T2DM was based on self-reports alone. The pooled estimates were larger than those of high-income countries, emphasizing that actions are needed to delay mortality in people with T2DM within the health-care systems in LA.

Limitations

Naturally, our study has some limitations. The assessment of other causes of death in a meta-analytic fashion was not possible, and neither could we estimate the risk using objectively measured glucose values as exposure variable. As outlined, only one study provided evidence on different causes of death.^{19,33} In addition, only one study was identified that provided risk estimates for fasting glucose as exposure variable.³⁵ Furthermore, in most studies T2DM was self-reported leading to a misclassification of the exposure variable as it has been shown that up to 50% of people with T2DM are not diagnosed in LA. This may lead to an overestimation of the real mortality rates. Lastly, another limitation may be the external validity of our results. We synthesised studies conducted in six countries in LA, a region with over thirty nations. Therefore, we are not certain that our pooled estimates would be the same for all the countries. Nevertheless, our results provide compelling and robust evidence of high mortality risk in people with T2DM in many LA countries. Finally, a limitation of this work is the assessment of diabetes as a direct cause of mortality. We argue that a more realistic way of assessing mortality due to an impaired glucose metabolism would be if glucose values (e.g., fasting or post-prandial) was the exposure variable and repeated measurements were available over time.

Available international evidence

Our results showed an increased risk of death for patients with T2DM similarly than previous studies conducted in high-income countries.³⁶⁻⁵⁴ However, the strength of the association seems to be

stronger in LA compared with other regions. A global analysis of pooled cohort studies in high-income countries reported a hazard ratio of 1.80 for all-cause mortality and 2.32 for cardiovascular mortality.³⁶ A number of cohort studies conducted in high-income countries reported similar figures,³⁷⁻⁴⁴ with hazard ratios for all-cause mortality ranging from 1.15 in Sweden and Scotland^{38,43} to 2.19 in England;⁴² whereas for cardiovascular mortality these estimates ranged from 1.14 in Sweden³⁸ to 3.28 in the UK.⁴¹

Several reasons may exist for the different strength of associations between high-income countries and our results. Overweight and obesity are very important risk factors and even aetiological factors for T2DM. However, people with T2DM in low- and middle-income countries may have been exposed to additional risk factors such as early life undernutrition,⁴⁵ low birthweight and early programming of physiological systems involved in the pathogenesis of diabetes leading to higher mortality rates.⁴⁶ These early-life features are usually more common in low- and middle-income countries than in high-income countries, therefore they may explain the differences in mortality risk. Further differences in T2DM related mortality between high- and middle-income countries may arise from the level of T2DM control. As the diabetes is less controlled in LA, it can be assumed that mortality due to T2DM may be higher.^{36,47-49} Metabolic control in general is also important because uncontrolled lipid profiles may increase mortality among people with T2DM.⁵⁰ Ethnicity, genetics as well as cultural and health backgrounds may account for differences in T2DM mortality.^{42,51,52} Along with ethnicity, socio-economic inequalities may influence different mortality risk as well through access to regular T2DM care and access to proper care when an acute outcome develops (e.g., cardiovascular events such as myocardial infarction).^{53,54}

However, our results are in line with those of middle-income countries. In China (upper-middle-income country) new diabetes cases had a 3.5-fold higher hazard of all-cause mortality. In addition, cardiovascular diseases were the leading cause with a HR of 3.5.⁵⁵ T2DM among Chinese elderly living in Hong Kong reported a HR of 1.56, and a cardiovascular disease HR of 1.84.⁵⁶ A systematic review of studies conducted in Nigeria (lower-middle-income country) estimated a mortality rate of 30.2 per 100,000 people.⁵⁷

Pooled LA risk estimates in context

A large population-based cohort study conducted in Mexico reported a higher mortality in T2DM patients whose metabolic control (HbA1c) was not optimal.³³ Their finding is consistent with other international studies.^{47,48} Although most LA countries offer access to health-care for the entire population regardless of their income (i.e., universal health coverage),⁵⁸ many people still face difficulties to access adequate diabetes care. In addition, patients with T2DM are not aware of their own responsibility to achieve good diabetes care.⁵⁹ An interdisciplinary approach involving health-care professionals, patient's societies, health-care centres and patients themselves should be organized to improve diabetes care and control, as it has been suggested for Hispanics in the US where they have worse diabetes profile than locals.⁶⁰

The pooled estimates for renal mortality were based on few reports. Studies on renal diseases are scant in low- and middle-income countries in general, particularly in patients at high risk such as people with T2DM. To our knowledge, our work is the first to provide pooled estimates for renal mortality among T2DM patients in LA. These results may increase awareness about the increased renal mortality in T2DM patients among public health decision makers

The analytic power of our sex- and age-stratified pooled risk estimates should be interpreted cautiously because these were based on few reports. Future studies should try to estimate the overall, as well as sex- and age-stratified risk estimates to obtain more precise information. Nevertheless, our pooled estimates appear to be consistent with international studies where the mortality risk was higher in women than in men.^{37,39-41,55,56} Likewise, other authors have reported larger risk estimates at younger than older ages.^{39,40,43}

Conclusions

Using the available evidence of population-based prospective cohort studies this work has identified and estimated the strength of the association between T2DM and mortality in LA. The higher mortality risk compared with high-income countries deserves close attention from health policies makers and clinicians to improve diabetes care and control hence preventing complications and delaying death. Future studies may provide further evidence on other causes of death (e.g., infectious diseases), risk estimates of objective measurements such as fasting glucose or HbA1c instead of self-reported diagnosis alone and gather more information of countries from which evidence is still unavailable.

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Table 1. Characteristics of included studies.

Author (publication year)	Study setting	Baseline year	Baseline sample size	Baseline age (years)	Baseline % men	Attrition %	Follow-up time	Diabetes definition	Baseline diabetes prevalence (%)
Molokhia, 2011	Plymouth, Trinidad & Tobago	1976-1978	832	43.7	42.0		30 years	Self-reported	21(men), 17(women)
Charles, 2018	Cuba	1996-2002	146,556	53 (SD: 13)			Until 2015	Self-reported	4(men), 7(women)
Lozano-Sparza, 2018	Mexico	2006-08	111,300	42 (SD: 7.5)	00.0		From 2006-15	Self-reported	5
Domiciano, 2016	Sao Paulo, Brazil	2005-07	839	73.3	30.8	69.0	4.06 (SD: 1.07) years	Self-reported, fasting blood glucose ≥ 126 mg/dL	20.7
Moreira, 2009	Southern Brazil	1989-91	982	43.1 (SD: 17)	44.3	90.0	5.3 (SD: 1.5) years	Self-reported or using diabetes therapy	4.2
Colpani, 2014	Passo Fundo, South Brazil	1995	358	44.3 (SD: 6.0)	00.0		13.4 (SD: 3.3) years	Previous diagnosis of diabetes mellitus was verified based on physician report or current use of diabetes therapy	3.9
Alegre-Díaz, 2016	Two districts in Mexico City	1998-2004	146,046	51.8	32.8		12 years	Self-reported, use of a diabetes therapy, or both	13

Hunt, 2011	Mexico City	1990-1992	2,281	47.3	41.2	95.9	15.1 years	Fasting/2-hour post load plasma glucose $\geq 160/200$ mg/dL, or reported physician-diagnosed diabetes and diabetes therapy	12.8
Rodriguez-Saldana, 2002	Centro Urbano Presidente Aleman (CUPA), southern Mexico City	1989	785		22.9			Fasting blood glucose ≥ 126 mg/dL; the diagnosis of diabetes was also established in subjects with a history of diabetes regardless of fasting blood glucose and in those who used diabetes therapy	
Herrington, 2018	Same study as in Alegre-Díaz								
Suemoto, 2015	Sao Paulo, Brazil	2000-2006	1,882	71.0	39.0	81.1	6.5 years	Self-reported by responding to the question "has a doctor or nurse ever told you that you have	16.6

									diabetes or high blood sugar levels?"	
Ruiz, 2003	Botucatu, Brazil	1983-1984	574			89.6	9 years	Self-reported	6.6	
Jesús Libre, 2014	Havana and Matanzas, Cuba	2003-2007	2,813	74.0	53.3	93.3		Self-reported that diabetes had been diagnosed by a physician and/or fasting blood glucose ≥ 7 mmol/L confirmed on two different days		
Downer, 2017	Puerto Rico	2002-2003	3,419	71.2	40.2	81.2	4 years	Participants who reported having been told by a doctor that s/he had diabetes	18.1	
de Oliveira, 2015	Minas Gerais, Southern Brazil	1997	1,382	68.8	38.5	97.3	5.45 years	Previous medical diagnosis and/or fasting blood glucose ≥ 126 mg/dL	18.5	
Bracco, 2018	Brazil							Self-reported		
PERU MIGRANT Study	Lima and Ayacucho, Peru	2008	976	48.0	47.2			Previous medical diagnosis and/or fasting blood glucose ≥ 126 mg/dL	4.1	

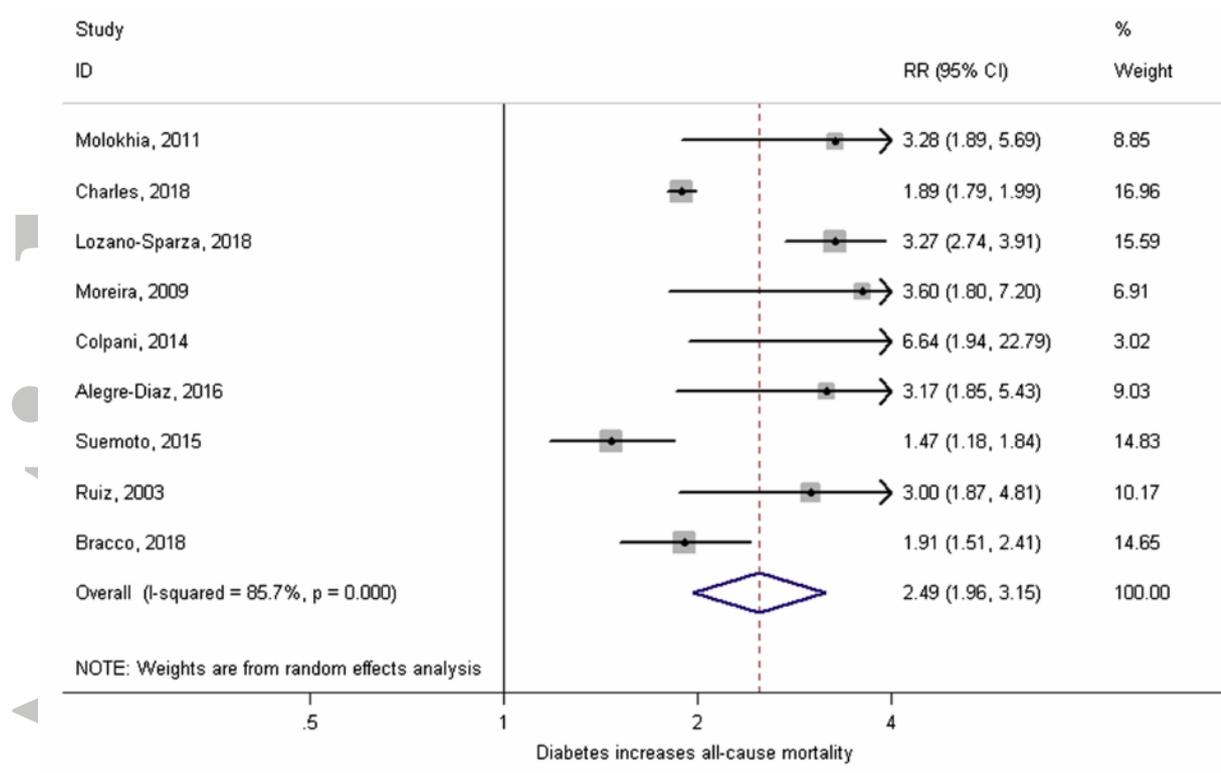


Figure 1A. All-cause mortality across studies assessing diabetes according to self-reported diagnosis.

Accepted

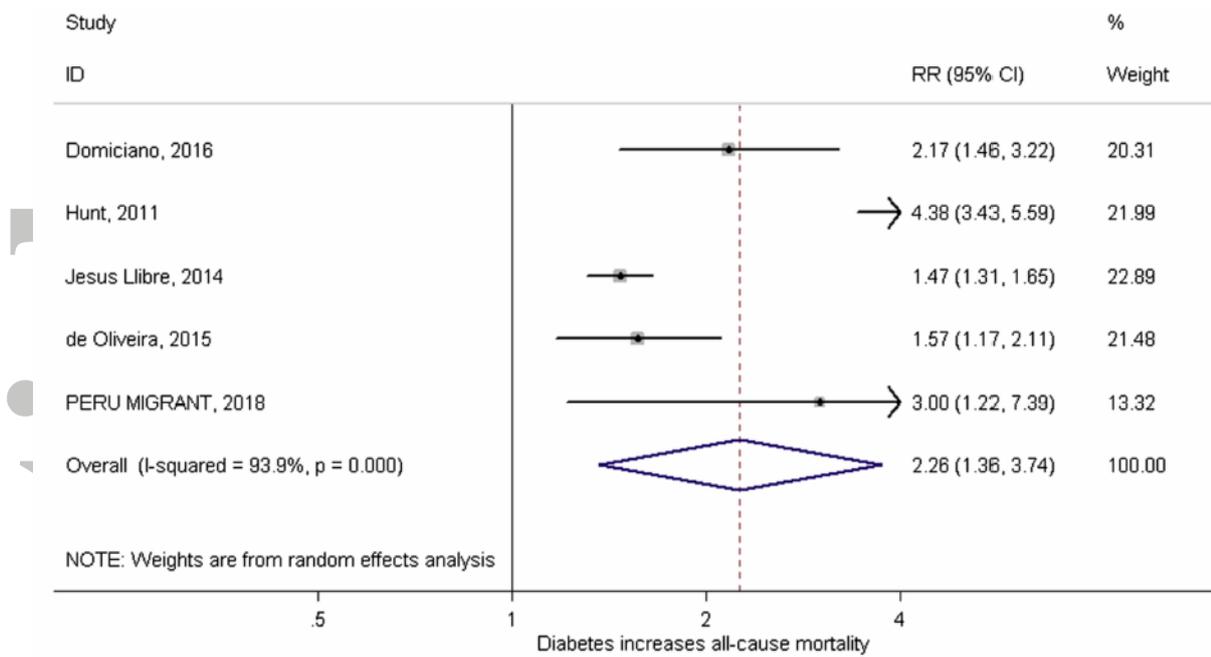


Figure 1B. All-cause mortality across studies assessing diabetes where the diagnosis of diabetes was based on a composite definition.

Accepted

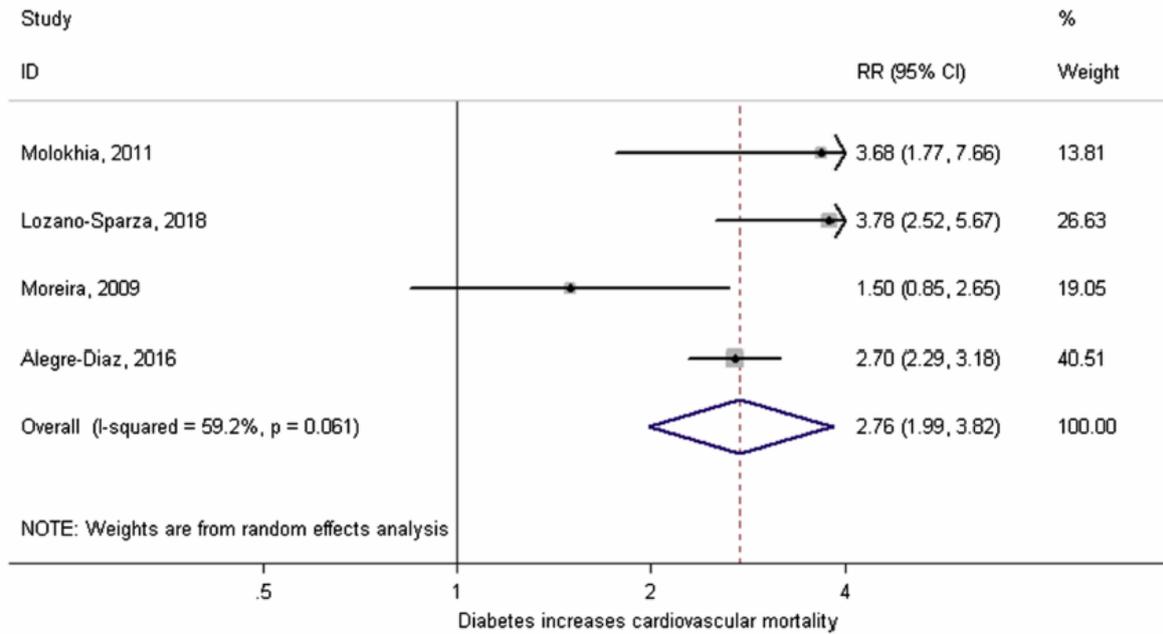


Figure 2. Cardiovascular mortality among studies assessing diabetes according to self-reported diagnosis.

Accepted

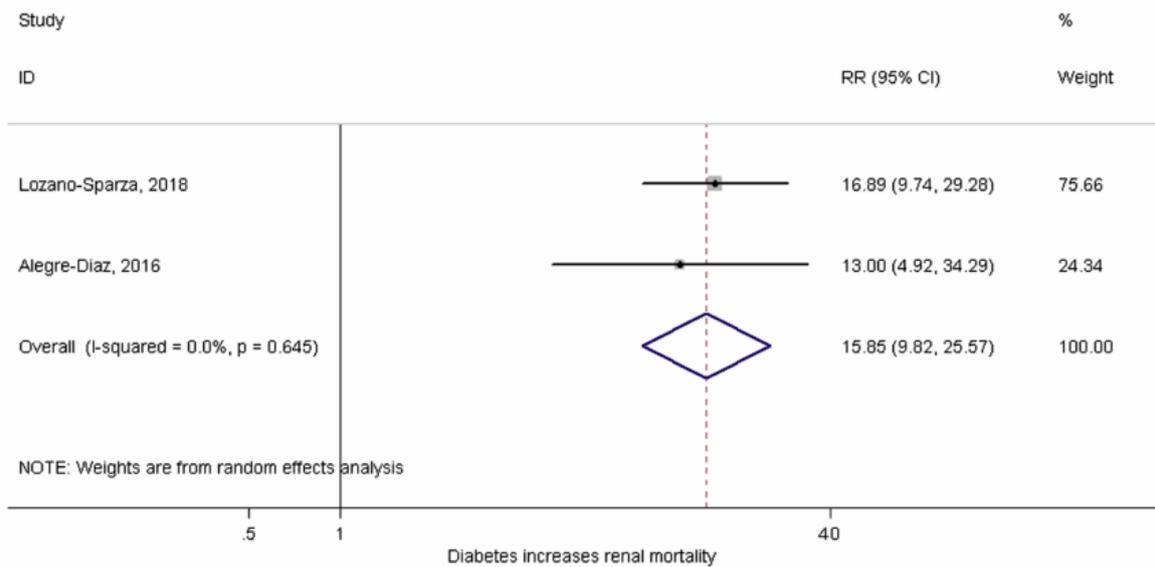


Figure 3. Renal mortality among studies assessing diabetes according to self-reported diagnosis.

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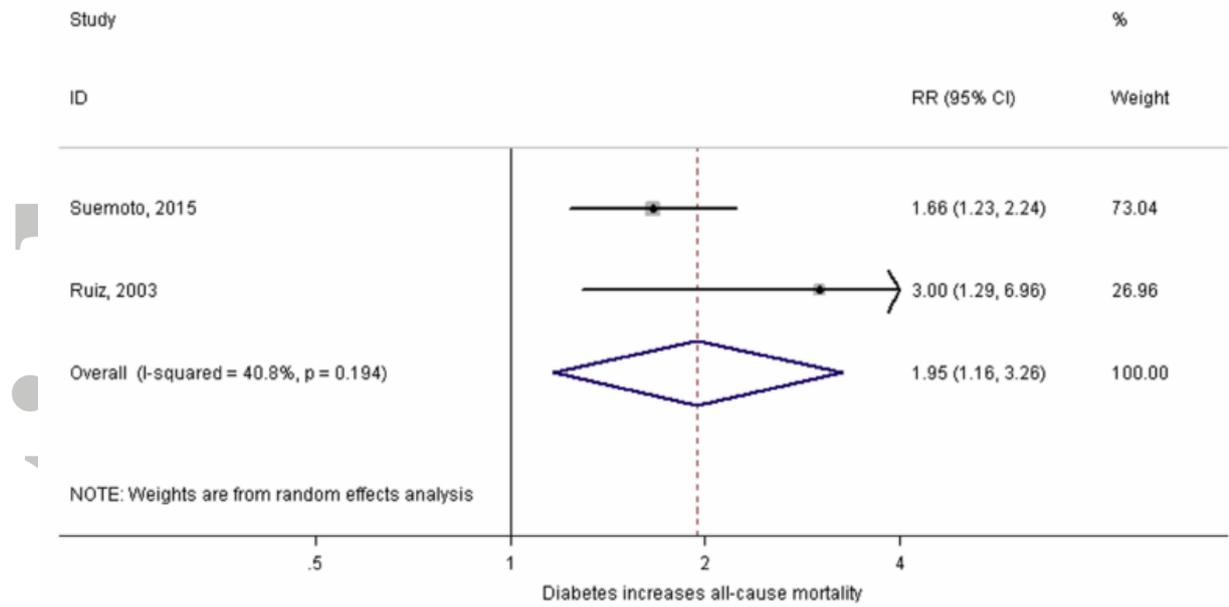


Figure 4A. All-cause mortality across studies assessing diabetes according to self-reported diagnosis in men.

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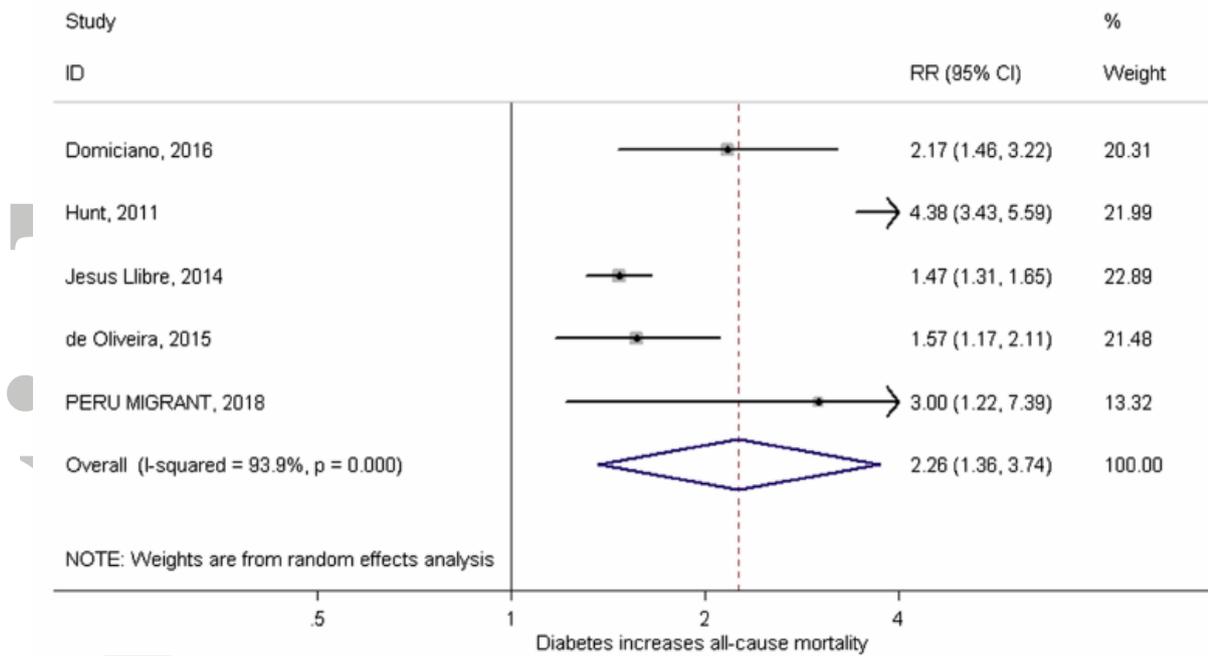


Figure 4B. All-cause mortality across studies assessing diabetes according to self-reported diagnosis in women.

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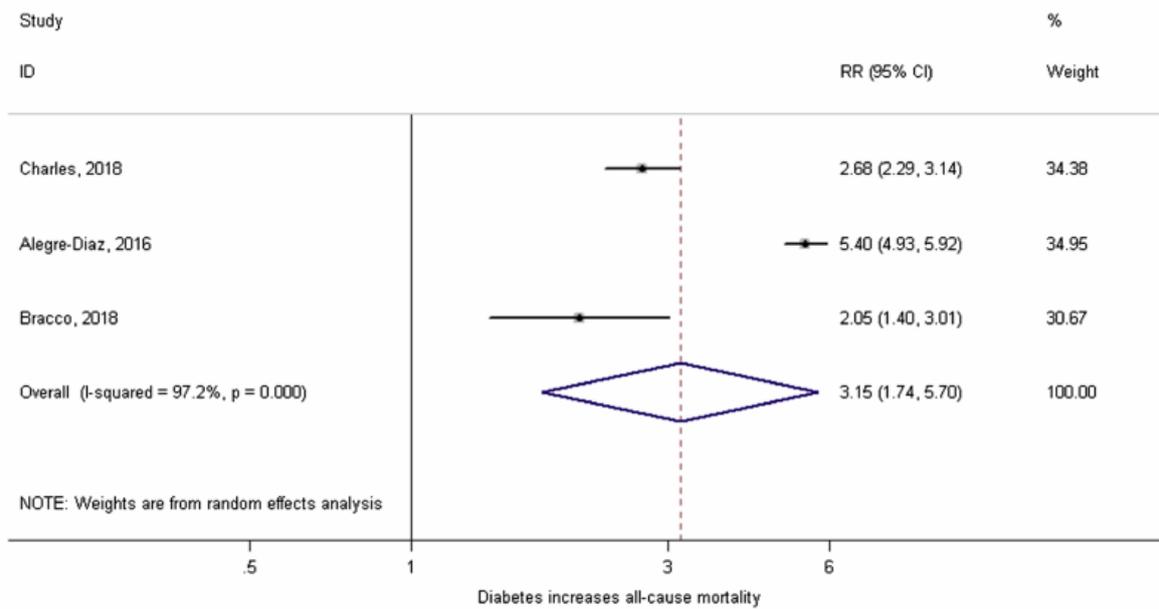


Figure 5A. All-cause mortality across studies assessing diabetes according to self-reported diagnosis in the age group 35-59 years-of-age.

Accepted

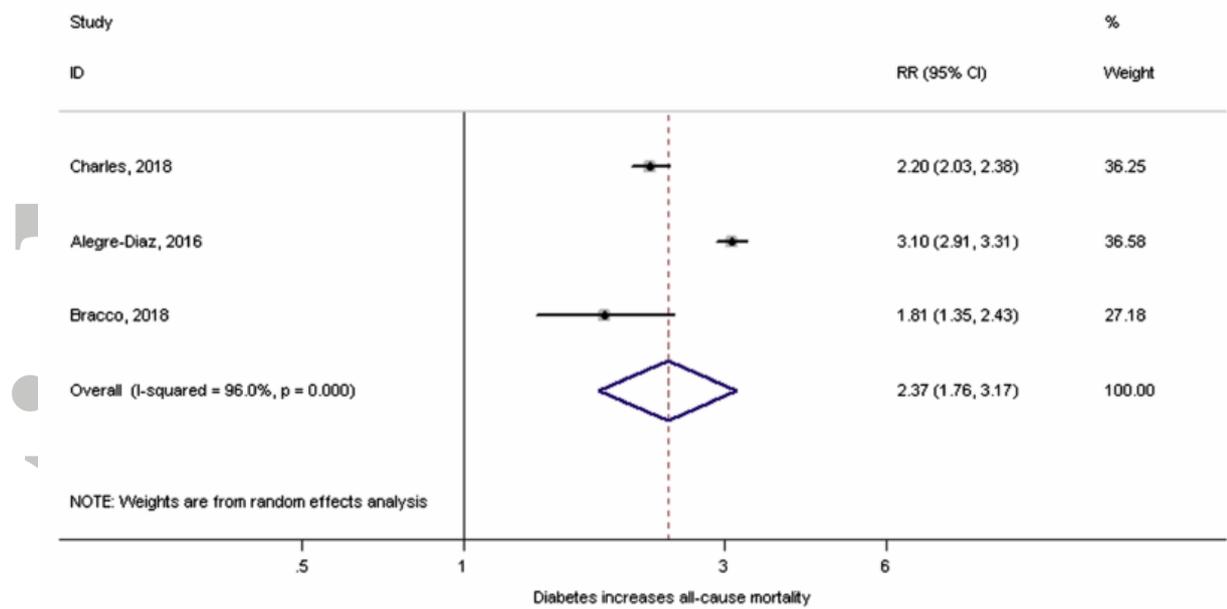


Figure 5B. All-cause mortality across studies assessing diabetes according to self-reported diagnosis in the age group 60-74 years-of-age.

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