General and Abdominal Adiposity and Mortality in Mexico City: prospective study of 150,000 adults

(Running title: Adiposity and mortality in Mexico City)

Louisa Gnatiuc[1] MSc,* Jesus Alegre-Díaz[2] MD,* Rachel Wade[1,3] MSc, Raúl Ramirez-Reyes[2], Roberto Tapia-Conyer[2] PhD, Adrián Garcilazo-Ávila[2] MSc, Erwin Chiquete[4] MD, Carlos Gonzáles-Carballo[2] MSc, Martha Solano-Sanchez[2] MSc, Robert Clarke[1] MD, Rory Collins[1] FRS, William G Herrington[1,3] MD, Michael Hill[1,3] PhD, Sarah Lewington[1,3] DPhil, Richard Peto[1] FRS, Jonathan R Emberson[1,3] PhD,† Pablo Kuri-Morales[2] MD†

* Joint first authors

† Joint last authors

[1] Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health (NDPH), University of Oxford, Oxford, UK

[2] School of Medicine, National Autonomous University of Mexico, Mexico City, Mexico

[3] MRC Population Health Research Unit, NDPH, University of Oxford, Oxford, UK

[4] Salvador Zubirán National Institute of Medical Sciences and Nutrition, Mexico City, Mexico

Correspondence:

Dr Jonathan Emberson

MRC-PHRU, Richard Doll Building, Old Road Campus,

Oxford OX3 7LF, United Kingdom

Email: jonathan.emberson@ndph.ox.ac.uk

or

Dr Jesus Alegre Díaz

School of Medicine, National Autonomous University of Mexico,

Mexico City, Mexico

Email: Jesus Alegre inypcjad@gmail.com

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Abstract

Background: Some reports suggest body-mass index (BMI) is not strongly associated with mortality in Hispanic populations.

Objective: To assess the causal relevance of adiposity to mortality in Mexican adults, avoiding reverse-causality biases.

Design: Prospective study.

Setting: Two Mexico City districts.

Participants: 159,755 adults aged ≥35 years at recruitment, followed for 14 years. Participants with glycated hemoglobin ≥7%, diabetes, or other chronic diseases were excluded.

Measurements: BMI, waist-hip ratio, waist circumference and cause-specific mortality. Cox regression, adjusted for confounders, yielded mortality hazard ratios (HRs) after ≥5 years of follow-up and before age 75.

Results: Among 115 400 included participants aged 35 to <75 years at recruitment, mean (SD) BMI was 28.0 (4.1) kg/m^2 in men and 29.6 (5.1) kg/m^2 in women. The association of BMI at recruitment with all-cause mortality was J-shaped, with minimum at 25 to <27.5 kg/m^2. Above 25 kg/m^2, each 5 kg/m^2 higher BMI was associated with 30% higher all-cause mortality (HR 1.30, 95% CI 1.24 to 1.36). This association was stronger at ages 40 to <60 years (1.40, 95% CI 1.30 to 1.49) than at ages 60 to <75 years, but was not materially affected by sex, smoking or other confounders. The associations of mortality with BMI and waist-hip ratio were comparably strong, and each was weakened only slightly by adjustment for the other. Waist circumference was strongly related to mortality, and remained so even after adjustment for BMI and hip circumference.

Limitations: Analyses were limited to mortality.

Conclusion: General and, particularly, abdominal adiposity are strongly associated with mortality in this Mexican population.

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Introduction

Adiposity is a major cause of death and disability (1, 2). Recent reports suggest that 0.6 billion adults would be classified by the WHO as being obese (defined as body-mass index [BMI] ≥30 kg/m^2) and 1.3 billion as being overweight (defined as BMI in the range 25 to <30 kg/m^2). In a meta-analysis of prospective studies, mostly in high-income countries, analyses of 4 million never-smokers without chronic disease who had survived more than 5 years after BMI was measured found that above a BMI of 25 kg/m^2 each additional 5 kg/m^2 of BMI was associated with about 31% higher all-cause mortality and 42% higher cardiovascular mortality (3).

Since most of the studies in that meta-analysis were undertaken, however, the prevalence of obesity has increased in many countries but vascular mortality has decreased, and the associations of BMI with mortality may be different in populations with substantially higher mean BMI than those originally studied, or in particular ethnic groups (4). Another meta-analysis that was restricted to Asian countries found that, among 0.7 million never-smokers who had survived more than 3 years, above a BMI of 25 kg/m^2 higher BMI was associated with substantially higher mortality only in East Asians, and not in South Asians (5). Similarly, a recent study in South India among 0.4 million adults without prior disease who had survived more than 2 years found that BMI was approximately unrelated to vascular mortality (6).

Two recent analyses of prospective studies of Hispanic adults (7,8) did not find overweight or obesity to be associated with higher all-cause mortality, but both studies were relatively small (17,000 and 39,000 respectively). Moreover, neither had allowed for the possible impact of “reverse causality” (whereby low BMI can be a consequence as well as a cause of disease). Additional studies that limit the effects

of reverse causality are needed to clarify the causal relevance of overweight and obesity to mortality in Hispanic populations, and to investigate whether, given BMI, indices of abdominal obesity such as the waist-hip ratio are of substantial further relevance to mortality. We report the associations of general and abdominal adiposity with all-cause and cause-specific mortality in a 14-year follow-up of 150,000 adults who were recruited into the Mexico City Prospective Study between 1998 and 2004 (9).

Methods

Recruitment and study oversight

Adults aged 35 years or older who were resident in two districts of Mexico City between 1998 and 2004 were invited to participate in a prospective study. We recorded age, sex, socioeconomic status, lifestyle factors (e.g., smoking status, alcohol intake, and physical activity), current medication and medical history.

Weight, height, and waist and hip circumferences were measured to the nearest 0.1 kg or 0.1 cm, respectively, using calibrated electronic scales, stadiometers and non-stretchable tapes. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured in the seated position. A 10 mL blood sample was collected from each participant. Plasma and buffy coat samples were sent to Oxford (UK) for long-term storage over liquid nitrogen. Glycated hemoglobin (HbA1c) was measured in buffy coat samples using a validated high-performance liquid chromatography method (10).

Study *population*

The main analyses excluded those who at recruitment already had HbA1c ≥7%, diabetes, renal disease, vascular disease, cancer, liver cirrhosis, or emphysema. They also excluded those who had missing or extreme values for any anthropometry measure (see **Table 1** footnote; 1.4% of otherwise eligible participants), missing or implausible covariate data (see *Statistical analyses*: 0.1% of otherwise eligible participants), age at recruitment ≥90 years, or uncertain vital status at the end of the follow-up (0.8% of otherwise eligible participants).

Mortality follow-up

Mortality was followed up to 1.1.2016 through probabilistic linkage to the Mexican electronic death registry, which has a high standard of quality and completeness (11). Field validation of over 7000 of these matched deaths confirmed the reliability of the matching process in over 95% of cases. The registry encoded all diseases mentioned on the death certificate using the International Classification of Diseases, 10th Revision (ICD-10) (12). Subsequently, study clinicians reviewed and, where necessary, re-coded the underlying cause of death (eg, accepting diabetes as the underlying cause only for deaths due to acute diabetic crises) (13).

Statistical analyses

The statistical methods are described fully in the **online appendix**. BMI was initially grouped into five WHO-defined categories: normal (18.5 to <25 kg/m²), overweight (25 to <30 kg/m²), obesity grade 1 (30 to <35 kg/m²), obesity grade 2 (35 to <40 kg/m²), and obesity grade 3 (40 to ≤60 kg/m²), excluding the few participants outside the BMI range 18.5 to 60 kg/m². However, since nearly two-thirds of the cohort were

in the ‘normal’ or ‘overweight’ categories, these two categories were further subdivided, yielding seven categories: 18.5 to <22.5 kg/m², 22.5 to <25 kg/m² (the reference group), 25 to <27.5 kg/m², 27.5 to <30 kg/m², 30 to <35 kg/m², 35 to <40 kg/m² and 40 to ≤60 kg/m². For comparability with the analyses of BMI, waist-hip ratio and the waist circumference were each subdivided into 7 categories that were prevalence-matched to the 7 BMI categories, again with the second group as the reference group.

To help limit the effects of reverse causality, those with certain prior diseases and those who died within 5 years of recruitment were excluded from the main analyses. These main analyses subdivide the remaining deaths and follow-up by 5-year ranges of ‘age at risk’, ie, by the age-ranges of follow-up in which those deaths occurred. The main analyses are of the deaths at ages 40 to <75 years (defined as “premature” deaths), but one subsidiary analysis is of the deaths at ages 75 to <90 years; this latter analysis includes participants aged 75 to <90 at recruitment in addition to adults aged 35 to <75 at recruitment in the primary analysis.

Cox regression, stratified by 5-year groups of age at risk, was used to assess the relevance of BMI, waist-hip ratio and waist circumference (each in the 7 groups described above) to mortality. The HR was estimated in each exposure group, after specifying one of these as the reference group with HR=1. The variance of the log risk in each group, including the reference group, was calculated (from the variances and covariances of the log HRs in all groups except the reference group) and used to obtain group-specific 95% CIs (14). Participants who did not die were censored at the end of the risk period under consideration (eg, on their 75th birthday for analyses

of deaths at ages 40 to <75 years) or the end of follow-up (January 1st, 2016). In analyses of cause-specific mortality (**Table S1**), participants who died from a cause other than that being analysed were censored at their date of death. These Cox regression analyses were all adjusted for sex, district of residence (two districts), self-reported highest attained level of education (university/college, high school, elementary school, other), leisure-time physical activity (none, up to twice weekly, at least three times weekly), smoking (never, former, current but not daily, daily [<10 cigarettes per day], daily [≥10 cigarettes per day]), and alcohol intake (none, former use, current use).

Subsequent analyses then included BMI as a continuous variable, with HRs estimated for 5 kg/m^2 higher BMI. With the same adjustment for covariates as above, these HRs were estimated separately for those with BMI <25 kg/m^2 and those with BMI ≥25 kg/m^2. All-cause mortality HRs associated with BMI were also estimated separately for deaths occurring 5 to <10 years after recruitment versus deaths occurring ≥10 years after recruitment. Other sensitivity analyses included exclusion of current or former smokers, exclusion of anyone with HbA1c concentration 6.5% to <7%, *inclusion* of those with previously-diagnosed diabetes but good glycemic control (defined as HbA1c <7%), and fitting the household of each participant as a 'random effect' (to allow for any clustering).

Analyses used SAS v9.4, STATA v13.1 and R v3.5.3 (www.r-project.org).

Study oversight and funding

Research ethics approval was obtained from the Mexican Health Ministry, Mexican National Council of Science and Technology, and the University of Oxford (UK). All participants provided written informed consent. The funding sources had no role in the design, conduct, analysis, or decision to submit the manuscript for publication.

Results

Participants

Of 112,333 eligible households visited, 106,059 (94%) yielded a total of 159,755 participants. Of these, 8907 were excluded because they were aged ≥90 years at recruitment or had a prior history of chronic diseases other than diabetes, and a further 4795 were excluded because they had extreme, uncertain or missing exposure, covariate or mortality outcome data (including 623 with BMI <18.5 kg/m^2 and 30 with BMI >60 kg/m^2). The remaining 146,053 included 19,068 with previously-diagnosed diabetes and 4888 others with HbA1c ≥7% at recruitment. Both groups were also excluded from the main analyses, leaving 122,097 participants, of whom 115,400 were aged 35 to <75 years and 6697 were aged 75 to <90 years at recruitment.

Adiposity and other baseline characteristics

Among the 115,400 participants aged 35 to <75 years, mean baseline BMI was 28.0 (SD 4.1) kg/m^2 in men and 29.6 (SD 5.1) kg/m^2 in women (**Table 1**). In both men and women, higher BMI was associated with lower levels of education, smoking, and leisure-time physical activity, and higher levels of blood pressure and HbA1c. The proportion with HbA1c in the range 6.5% to <7% increased from 1% in the lowest BMI group (18.5 to <25 kg/m^2) to 7% in the highest group (40 to 60

kg/m^2). Similar patterns were observed for groups defined by waist-hip ratio or by waist circumference (**Tables S2 and S3**). BMI was highly correlated with waist circumference (age-adjusted r=0.83 in men and 0.83 in women), but less strongly correlated with the waist-hip ratio (r=0.45 and 0.23, respectively).

Adiposity and all-cause mortality

Figure 1 shows the associations of BMI, waist-hip ratio and waist circumference with all-cause mortality. The analyses are restricted to deaths at ages 40 to <75 years among participants without diabetes or other chronic disease at recruitment. For the seven baseline groups defined by BMI in the ranges 18.5 to <22.5 kg/m², 22.5 to <25 kg/m² (the reference group), 25 to <27.5 kg/m², 27.5 to <30 kg/m², 30 to <35 kg/m², 35 to <40 kg/m² and 40 to 60 kg/m², respectively, the HRs (and group-specific 95% confidence intervals) were 1.12 (CI, 0.95 to 1.31), 1.00 (CI, 0.90 to 1.12), 0.90 (CI, 0.82 to 0.98), 1.00 (CI, 0.92 to 1.08), 1.16 (CI, 1.08 to 1.24), 1.62 (CI, 1.45 to 1.81) and 2.10 (CI, 1.78 to 2.49). Thus, BMI appeared to be inversely related to mortality below 25 kg/m^2, although this was based on only 486 deaths. Above 25 kg/m^2, however, there were 2304 deaths, the range of BMI was wider, and BMI was highly significantly positively related to all-cause mortality, with each 5 kg/m^2 higher BMI associated with about 30% higher mortality (HR 1.30, 95% CI 1.24 to 1.36) (**Table 2**). By comparison, the relationship between waist-hip ratio and all-cause mortality appeared to be continuous and approximately 'log-linear' throughout the range studied. Finally, the relationship between waist circumference and all-cause mortality appeared to be curvilinear.

Figure 2 shows that the positive association of BMI with all-cause mortality in the BMI range above 25 kg/m^2 was stronger at younger than at older ages, with each 5 kg/m^2 higher BMI being associated with 40% higher mortality at ages 40 to <60 years (HR 1.40, 95% CI 1.30 to 1.49), 24% higher mortality at ages 60 to <75 years (HR 1.24, 95% CI 1.17 to 1.31) and 21% higher mortality at ages 75 to <90 years (HR 1.21, 95% CI 1.15 to 1.28) (p for effect modification across these three age ranges 0.003). Within each age range, however, the associations of BMI with all-cause mortality were similar in men and women, and were not materially affected by district, smoking, education, physical activity or alcohol intake (**Figure S1**). When the positive association of BMI with mortality at ages 40 to <75 was subdivided by period of follow-up, it appeared to be stronger for deaths occurring 10 or more years after recruitment (HR 1.37, 95% CI 1.28 to 1.46) than for deaths occurring 5 to <10 years after recruitment (HR 1.24, 95% CI 1.17 to 1.32).

Figure 3 explores the independent relevance of the three different markers of adiposity to mortality at ages 40 to <75 years. As BMI and waist-hip ratio were somewhat correlated, adjustment for either of these two measures reduced the association of the other with all-cause mortality, but in both cases strong relationships remained. As our measurement of waist circumference was strongly correlated with BMI, about three-quarters of the variation in it was accounted for by the variation in BMI and hip circumference. Nevertheless, adjustment for BMI and hip circumference somewhat strengthened the association between waist circumference and all-cause mortality, making it approximately log-linear throughout its full range.

BMI and disease-specific mortality

For different underlying causes of death at ages 40 to <75 years, **Table 2** shows the HRs associated with a 5 kg/m^2 higher BMI separately for the ranges 18.5 to <25 kg/m^2 and 25 to ≤60 kg/m^2 (see **Figure S2** for the shapes of these associations). The numbers of deaths from particular causes in the BMI range 18.5 to <25 kg/m^2 were too small for statistical stability, but above this BMI range strong positive associations were observed for mortality from vascular disease, renal disease/acute diabetic crisis, hepatobiliary disease, respiratory disease, and infection, though not from cancer or the composite of all other, ill-defined or external causes. For the combination of death from any vascular or metabolic cause (ie, vascular, renal/acute diabetic, or hepatobiliary), each 5 kg/m^2 higher BMI above 25 kg/m^2 was associated with 40% higher mortality (death HR 1.40, 95% CI 1.32 to 1.49).

Cause-specific HRs associated with BMI were consistent when analyses were restricted to never smokers; when participants with HbA1c 6.5% to <7% were excluded; or when those with previously-diagnosed diabetes but good glycemic control (defined as a glycated hemoglobin <7%) were *included* (**Table S4**). Results were also virtually identical when analyses were repeated using a multi-level model with household fitted as a random effect to allow for any clustering (**Table S5**).

Reverse causality

To help assess the causal effects of adiposity and limit the extent to which associations of baseline adiposity with mortality are distorted by any effects of diabetes or other diseases on the baseline measurements, the main analyses were of mortality more than 5 years after the baseline measurements and excluded participants who at recruitment had HbA1c ≥7%, previously-diagnosed diabetes or

other chronic disease. **Figures S3 and S4** show the substantial biases that would have resulted if such exclusions had not been implemented. For BMI and for waist circumference the associations with all-cause mortality would have become strikingly 'U-shaped', with little difference between those in the top and bottom groups (**Figure S3**). This would have been qualitatively different from the associations in the main analyses (**Figure 1**). For, among participants who already had HbA1c ≥7% or diabetes at recruitment there was a strong inverse association of BMI with all-cause mortality (**Figure S4**).

Discussion

Both general and abdominal adiposity were strongly associated with all-cause mortality in this large study of Mexican adults. Each 5 kg/m^2 higher BMI above 25 kg/m^2 was associated with 30% higher all-cause mortality. In this BMI range the association with all-cause mortality was stronger at younger than at older ages, but at any given age it was of similar strength in men and in women. The waist-hip ratio was comparably strongly associated with all-cause mortality, and the associations of waist-hip ratio and of BMI with mortality were largely independent of each other, each becoming only slightly weaker on adjustment for the other.

Surprisingly, however, after adjustment for BMI and hip circumference, the association of low waist circumference with low mortality was strengthened, making the adjusted relationship of waist circumference to mortality approximately log-linear throughout its entire range. This means that although knowledge of height, weight and hip circumference can provide a reasonably accurate prediction of waist circumference (accounting for about three-quarters of its variance), at all levels of

waist circumference the difference between the actual and predicted waist circumference remains strongly associated with mortality. This supports previous evidence that *central* adiposity is of particular importance (15).

Poorly controlled diabetes, which is common in Mexico (13, 16), can cause weight loss, resulting in a misleadingly inverse association between glycated hemoglobin and BMI, and a misleadingly inverse association between BMI and mortality in adults with diabetes (**Figure S4**). To help avoid misleading associations, our analyses excluded those who at recruitment already had glycated hemoglobin elevation or diabetes and those who died within 5 years, and sensitivity analyses illustrate the importance of these exclusions. The risks associated with being overweight or obese in our main analyses are therefore consistent with those in appropriate analyses of studies in Western populations (3, 15, 17-18). They differ substantially, however, from previous claims, based on analyses without the necessary exclusions, that in Hispanic populations being overweight or obese was not associated with higher risks of all-cause mortality (the so-called 'Hispanic paradox') (7, 8). This apparent discrepancy may chiefly reflect inadequate control in previous analyses for the extent to which diabetes or other disease processes can distort the relationship between BMI and mortality.

With direct rather than self-reported anthropometry, and the above precautions against being substantially misled by reverse causality, this study can assess reasonably reliably the separate and joint associations of mortality with BMI and with the waist-hip ratio. Although it can not rule out some residual confounding, and lacks other methods of assessing abdominal adiposity, its chief strengths include its size

and duration (yielding many deaths for analysis) and the availability of information on a wide range of relevant factors (although not yet lipids, markers of renal function or other biochemical markers). Its chief limitation is the lack of information on the incidence of non-fatal diabetes, renal and vascular disease and its reliance on the death certificate; but, the main analyses are of all-cause mortality. There was also an insufficient number of cancer deaths to be able to investigate site-specific cancer reliably. As in many prospective studies, participants were probably somewhat healthier than the general population, not least because the analyses exclude those with diabetes or other chronic diseases at recruitment.

The HRs in this report describe the *relative* impact of various measures of adiposity on mortality, but not the *absolute* excess risks of premature death. **Figure 4** shows what our HR of 1.30 per 5 kg/m^2 higher BMI would imply for the dependence on BMI of the probability of survival from age 40 years, if the 2016 Mexican national death rates correspond to what would be seen in a population with BMI 29 kg/m^2. Compared with a BMI of 25 kg/m^2, the reduction in adult life expectancy from age 40 years would be about 3 years at a BMI of 30 kg/m^2 but nearly 10 years at a BMI of 40 kg/m^2.

Obesity is a major cause of diabetes, and in Mexico diabetes is a major cause of premature death and disability, accounting for at least one-third of Mexican deaths at ages 35 to 74 years (13). Although we assessed only mortality, our findings suggest that even a moderate population-wide reduction in average adiposity levels could substantially reduce both morbidity and mortality in middle age. In addition to their relevance to Mexicans, these findings are likely to be relevant to other Hispanic

populations, including many millions of Mexican-Americans (as they refute previous suggestions of a 'Hispanic obesity paradox'), although the quantitative relevance of obesity will depend on the distributions of the causes of death in those populations (particularly those most closely related to adiposity) and on the quality of medical treatment, particularly for diabetes and renal and vascular disease.

Overall, in this large prospective study of Mexican adults with high levels of overweight and obesity, we found that both general and abdominal adiposity were major risk factors for premature death, with strengths of association that were comparable with those observed in high-income populations. We also found that, given BMI, the waist-hip ratio remains of substantial additional relevance to mortality, suggesting that central obesity is particularly harmful.

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Author contributions

JAD, RCo, RP, RTC, and PKM established the cohort. JAD, LG, RRR, MSS, WH, MH, RTC, PKM and JRE gathered the data. LG, RCl and JRE specified the analyses, LG and RW conducted the analyses, and LG and JRE wrote the first draft of the paper. All authors suggested revisions to the report and provided consent for publication. LG and JRE had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

References

1. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1345–1422

2. The Global Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 Years. N Engl J Med 2017; 377: 13–27.

3. The Global BMI Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016; 388: 776–86.

4. Heymsfield SB, Peterson CM, Thomas DM, Heo M, Schuna Jr JM. Why are there race/ethnic differences in adult body mass index–adiposity relationships? A quantitative critical review. Obesity Rev. 2016; 17: 262–75.

5. Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K et al. Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med 2011; 364: 719–29.

6. Gajalakshmi V, Lacey B, Kanimozhi V, Sherliker P, Peto R, Lewington S. Body-mass index, blood pressure, and cause-specific mortality in India: a prospective cohort study of 500 810 adults. Lancet Glob Health 2018; 6: e787–94.

7. Fontaine KR, McCubrey R, Mehta T, Pajewski NM, Keith SW, Bangalore SS et al. Body mass index and mortality rate among Hispanic adults: a pooled analysis of multiple epidemiologic data sets. Int J Obes. 2012; 36: 1121–26.

8. Mehta T, McCubrey R, Pajewski NM, Keith SW, Allison DB, Crespo CJ et al. Does obesity associate with mortality among Hispanic persons? Results from the National Health Interview Survey. Obesity 2013; 21: 1474–77.

9. Tapia-Conyer R, Kuri-Morales P, Alegre-Díaz J, Whitlock G, Emberson J, Clark S et al. Cohort profile: the Mexico City Prospective Study. Int J Epidemiol 2006; 35: 243–49.

10. Youngman LD, Clark S, Manley S, Peto R, Collins R. Reliable measurement of glycated hemoglobin in frozen blood samples: implications for epidemiologic studies. Clin Chem 2002; 48: 1627–29.

11. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. World Health Organ. 2005; 83: 171–77.

12. International statistical classification of diseases and related health problems: 10th revision (ICD-10). Vol.2. Geneva: World Health Organisation, 2004.

13. Alegre-Díaz J, Herrington W, López-Cervantes M, Gnatiuc L, Ramirez R, Hill M et al. Diabetes and Cause-Specific Mortality in Mexico City. N Engl J Med 2016; 375: 1961–71.

14. Plummer M. Improved estimates of floating absolute risk. Stat Med 2004; 23: 93–104.

15. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008; 359: 2105–20

16. Flores-Hernández S, Saturno-Hernández PJ, Reyes-Morales H, Barrientos-Gutiérrez T, Villalpando S, Hernández-Ávila M. Quality of diabetes care: the challenges of an increasing epidemic in Mexico — results from two national health surveys (2006 and 2012). PLoS One 2015; 10: e0133958.

17. The Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011; 377: 1085–95.

18. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009; 7: 1083–96.

Figures

Figure 1: Relevance of BMI, waist circumference and waist-hip ratio to all-cause mortality at ages 40 to <75 years

BMI=Body mass index, CI=Confidence interval, HR=Mortality hazard ratio. Analyses exclude participants with HbA1c at recruitment ≥7%, diabetes or other chronic disease (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema), and all deaths in the first 5 years of follow-up. The seven BMI categories represent BMI in the ranges 18.5 to <22.5 kg/m², 22.5 to <25 kg/m² (the reference group), 25 to <27.5 kg/m², 27.5 to <30 kg/m², 30 to <35 kg/m², 35 to <40 kg/m²; and 40 to 60 kg/m², and are plotted against the mean BMI in each group. For waist-hip ratio and waist circumference, the 7 groups are prevalence-matched to the 7 BMI categories. The vertical lines through each point represent group-specific 95% confidence intervals with the area of each square plotting symbol proportional to the amount of statistical information. For each group, the HR is shown above and the number of deaths below the square. HR estimates are stratified by age-at-risk (in five-year ranges), and adjusted for sex, district of residence, highest attained level of education, leisure-time physical activity, smoking status and alcohol intake.

Figure 2. Age and sex-specific relevance of BMI (in the range 25 to 60 kg/m^2) to all-cause mortality at ages 40 to <90 years

BMI=Body mass index, CI=Confidence interval, HR=Mortality hazard ratio. Analyses exclude participants with HbA1c at recruitment ≥7%, diabetes or other chronic disease (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema), and all deaths in the first 5 years of follow-up. All analyses include participants who were aged 35 to <75 years at recruitment except for analyses of deaths occurring between ages 75 to < 90 years which also included participants aged 75 to < 90 years at recruitment. Within each age-at-risk group shown, the sex-specific HR estimates are stratified by age-at-risk (in five-year ranges), and adjusted for district of residence, highest attained level of education, leisure-time physical activity, smoking status and alcohol intake. The overall HR estimates are additionally adjusted for sex. A test for trend in the log HR across the three age-at-risk categories shown yields a chi-squared statistic of 8.9 on 1df (p =0.003).

Figure 3: Relevance of BMI, waist circumference and waist-hip ratio to all-cause mortality at ages 40 to <75 years, after additional adjustment for other markers of adiposity

BMI=Body mass index, CI=Confidence interval, HR=Mortality hazard ratio. Analyses exclude participants with HbA1c at recruitment ≥7%, diabetes or other chronic disease (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema), and all deaths in the first 5 years of follow-up. The seven BMI categories represent BMI in the ranges 18.5 to <22.5 kg/m², 22.5 to <25 kg/m² (the reference group), 25 to <27.5 kg/m², 27.5 to <30 kg/m², 30 to <35 kg/m², 35 to <40 kg/m²; and 40 to 60 kg/m², and are plotted against the mean BMI in each group. For waist-hip ratio and waist circumference, the 7 groups are prevalence-matched to the 7 BMI categories. The vertical lines through each point represent group-specific 95% confidence intervals with the area of each square plotting symbol proportional to the amount of statistical information. For each group, the HR is shown above and the number of deaths below the square. HR estimates are stratified by age-at-risk (in five-year ranges), and adjusted for sex, district of residence, highest attained level of education, leisure-time physical activity, smoking status and alcohol intake. In addition, the BMI results are adjusted for the waist-hip ratio, the waist-hip ratio results are adjusted for BMI, and the waist circumference results are adjusted for hip circumference and BMI (with the adjustments using the same categories as shown above).

Figure 4: Hypothetical effect of a mortality hazard ratio of 1.30 per 5 kg/m^2 higher BMI on survival from age 40 to 75 years, at 2016 Mexican mortality rates

BMI=Body mass index. Taking the age- and sex-specific national death rates for Mexico for the year 2016 to correspond to a population with mean BMI 29 kg/m^2, the corresponding death rates for a population with mean BMI *x* kg/m^2 higher (or lower) than 29 kg/m^2 would then differ from these rates by the factor $1.30^{x/5}$ (or its inverse). Plotted are the resulting survival patterns for populations with mean BMI 25 kg/m^2, 30 kg/m^2, 35 kg/m^2 and 40 kg/m^2.

Postal addresses of all authors

Louisa Gnatiuc, Rachel Wade, Robert Clarke, Rory Collins, William Herrington, Michael Hill, Sarah Lewington, Richard Peto, Jonathan Emberson
Clinical Trial Service Unit and Epidemiological Studies Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford, OX3 7LF, UK

Jesus Alegre-Díaz, Raúl Ramirez-Reyes, Adrián Garcilazo-Ávila, Carlos Gonzáles-Carballo, Martha Solano-Sanchez, Roberto Tapia-Conyer, Pablo Kuri-Morales
Facultad de Medicina UNAM, Avenida Universidad 3000, Cd. Universitaria, 04510 Coyoacan, Mexico City, Mexico

Erwin Chiquete
The Salvador Zubirán National Institute of Medical Sciences and Nutrition, Mexico City, Mexico