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General and Abdominal Adiposity and Mortality in Mexico City

Prospective Study of 150 000 Adults

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

Background: Some reports suggest that 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: 2 Mexico City districts.

Participants: 159 755 adults aged 35 years and older at recruitment, followed for up to 14 years. Participants with a hemoglobin A_{1c} level of 7% or greater, diabetes, or other chronic diseases were excluded.

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

Results: Among 115 400 participants aged 35 to <75 years at recruitment, mean BMI was 28.0 kg/m^2 (SD, 4.1 kg/m^2) in men and 29.6 kg/m^2 (SD, 5.1 kg/m^2) in women. The association of BMI at recruitment with all-cause mortality was J-shaped, with the minimum at 25 to <27.5 kg/m^2. Above 25 kg/m^2, each 5-kg/m^2 increase in BMI was associated with a 30% increase in all-cause mortality (HR, 1.30 [95% CI, 1.24 to 1.36]). This association was stronger at ages 40 to <60 years (HR, 1.40 [CI, 1.30 to 1.49]) than at ages 60 to <75 years (HR, 1.24 [CI, 1.17 to 1.31]) but was not materially affected by sex, smoking, or other confounders. The associations of mortality with BMI and waist-to-hip ratio were similarly 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 were strongly associated with mortality in this Mexican population.

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For author affiliations, see end of text.

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* Ms. Gnatiuc and Dr. Alegre-Díaz share first authorship.

† Drs. Emberson and Kuri-Morales share last authorship.

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

Since most of those studies were completed, however, the prevalence of obesity has increased in many countries, whereas vascular mortality has decreased. Further, 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, further increases in BMI were associated with substantially higher mortality in East Asians but not in South Asians (5). Similarly, a recent study in South India among 0.4 million adults without previous disease who had survived longer than 2 years found that BMI was approximately unrelated to vascular mortality (6).

Two recent analyses of prospective studies in Hispanic adults found no association between overweight or obesity and higher all-cause mortality, although both studies were relatively small (17 000 and 39 000 participants, respectively) (7, 8). Moreover, neither study allowed for the possible effect of "reverse causality" (whereby low BMI may be a consequence as well as a cause of disease). Studies limiting 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 waist-to-hip ratio, have substantial further relevance to mortality. We report the associations between general and abdominal adiposity and all-cause and cause-specific mortality during a 14-year follow-up of 150 000 adults who participated in the Mexico City Prospective Study between 1998 and 2004 (9).

See also:

Web-Only
Supplement

Table 1. Characteristics of 115 400 Participants Aged 35 to <75 Years at Recruitment, by Sex and BMI

Characteristic	Men, by BMI					
	18.5 to <25 kg/m² (*n* = 8346)	25 to <30 kg/m² (*n* =18 564)	30 to <35 kg/m² (*n* = 8462)	35 to <40 kg/m² (*n* = 1578)	40 to ≤60 kg/m² (*n* = 394)	All Men (*n* = 37 344)
Mean age (SD), *y*	50 (11)	50 (11)	50 (10)	50 (10)	48 (10)	50 (11)
Demographic and lifestyle characteristics, *n (%)*						
Resident of Coyoacán	4220 (51)	8395 (45)	3395 (40)	551 (35)	161 (41)	16 722 (45)
University/college educated	2434 (29)	5243 (28)	1970 (23)	357 (23)	97 (25)	10 101 (27)
Current tobacco use	4755 (57)	9447 (51)	4270 (50)	785 (50)	205 (52)	19 462 (52)
Current alcohol use	7096 (85)	15 723 (85)	7163 (85)	1343 (85)	339 (86)	31 664 (85)
Any regular leisure-time physical activity	2771 (33)	6180 (33)	2312 (27)	324 (21)	81 (21)	11 668 (31)
Mean physical measurements (SD)						
Height, *cm*	166 (7)	165 (7)	165 (7)	164 (7)	164 (9)	165 (7)
Weight, *kg*	63 (7)	75 (7)	87 (8)	100 (10)	117 (15)	76 (13)
BMI, *kg/m²*	23.1 (1.5)	27.5 (1.4)	31.9 (1.3)	36.8 (1.3)	43.1 (3.2)	28.0 (4.1)
Waist circumference, *cm*	86 (6)	95 (6)	104 (7)	114 (8)	127 (12)	96 (10)
Hip circumference, *cm*	94 (5)	100 (5)	107 (6)	114 (7)	126 (12)	101 (8)
Waist-to-hip ratio	0.91 (0.06)	0.94 (0.05)	0.97 (0.06)	1.00 (0.06)	1.01 (0.08)	0.95 (0.06)
Waist-to-height ratio	0.52 (0.04)	0.57 (0.04)	0.63 (0.04)	0.70 (0.05)	0.77 (0.06)	0.58 (0.06)
SBP, *mm Hg*	123 (14)	127 (14)	130 (15)	135 (16)	138 (18)	127 (15)
DBP, *mm Hg*	82 (9)	84 (9)	86 (10)	89 (10)	91 (11)	84 (10)
HbA_{1c} level						
Mean (SD), *%*	5.4 (0.3)	5.5 (0.4)	5.6 (0.4)	5.7 (0.4)	5.8 (0.5)	5.5 (0.4)
6.5% to <7%, *n (%)*	48 (1)	241 (1)	238 (3)	74 (5)	28 (7)	629 (2)
Long-term medication use, *n (%)*						
Any antihypertensive	347 (4)	1323 (7)	898 (11)	203 (13)	75 (19)	2846 (8)
Any antithrombotic	127 (2)	382 (2)	194 (2)	30 (2)	11 (3)	744 (2)
Any lipid-lowering agent	28 (<0.5)	80 (<0.5)	35 (<0.5)	5 (<0.5)	2 (1)	150 (<0.5)

BMI = body mass index; DBP = diastolic blood pressure; HbA_{1c} = hemoglobin A_{1c}; SBP = systolic blood pressure.
* Participants were classified into standard World Health Organization BMI categories, but for analyses of all-cause mortality, the normal (BMI 18.5 to <25 kg/m²) and overweight (BMI 25 to <30 kg/m²) categories were divided further. Table excludes participants with previously diagnosed diabetes or an HbA_{1c} level ≥7% at recruitment; those with other chronic diseases (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema) at recruitment; those with missing data on any analysis covariate (sex, district of residence, educational level attained, smoking status, alcohol intake, or leisure-time physical activity), comprising 0.1% of otherwise eligible participants; those with uncertain follow-up (0.8% of otherwise eligible participants); and those with missing data for any anthropometry measure (0.7% of otherwise eligible participants) or extreme measures of anthropometry: height <120 or >200 cm, weight <35 or >250 kg, waist circumference <60 or >180 cm, hip circumference <70 or >180 cm, waist-to-hip ratio <0.5 or >1.5, or BMI <18.5 or >60 kg/m² (0.7% of otherwise eligible participants).

METHODS

Recruitment and Study Oversight

Adults aged 35 years or older who were residents of 2 Mexico City districts between 1998 and 2004 were invited to participate in this prospective study. We recorded age, sex, socioeconomic status, lifestyle factors (such as smoking, alcohol intake, and physical activity), current medications, and medical history.

Calibrated electronic scales, stadiometers, and nonstretchable tape were used to measure weight (to the nearest 0.1 kg), height (to the nearest 0.1 cm), and waist and hip circumference (also to the nearest 0.1 cm), respectively. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured with the participant seated. A 10-mL blood sample was collected from each participant. Plasma and buffy coat samples were sent to Oxford (United Kingdom) for long-term storage over liquid nitrogen. Hemoglobin A_{1c} (HbA_{1c}) was measured in buffy coat samples by using a validated high-performance liquid chromatography method (10).

Study Population

The main analyses excluded participants with an HbA_{1c} level of 7% or higher at recruitment and those with previous diagnoses of diabetes, renal disease, vascular disease, cancer, liver cirrhosis, or emphysema. Participants who had missing or extreme values for any anthropometry measure (Table 1 footnote) (1.4% of otherwise eligible participants), had missing or implausible covariate data (Statistical Analysis section) (0.1% of otherwise eligible participants), were aged 90 years or older at recruitment, or had uncertain vital status at the end of follow-up (0.8% of otherwise eligible participants) were also excluded.

Mortality Follow-up

Mortality was tracked up to 1 January 2016 through probabilistic linkage to the Mexican electronic death registry, which has a high standard of quality and completeness (11). Field validation of more than 7000 matched deaths confirmed the reliability of the matching process in more than 95% of cases. The registry encodes all diseases mentioned on the death certifi-

Table 1–Continued

Characteristic	Women, by BMI					
	18.5 to <25 kg/m² (*n* = 13 831)	25 to <30 kg/m² (*n* = 31 795)	30 to <35 kg/m² (*n* = 21 780)	35 to <40 kg/m² (*n* = 7827)	40 to ≤60 kg/m² (*n* = 2823)	All Women (*n* = 78 056)
Mean age (SD), *y*	47 (11)	49 (10)	50 (10)	50 (10)	50 (10)	49 (10)
Demographic and lifestyle characteristics, *n (%)*						
Resident of Coyoacán	6606 (48)	13 008 (41)	7689 (35)	2537 (32)	877 (31)	30 717 (39)
University/college educated	3166 (23)	4605 (14)	2058 (9)	641 (8)	223 (8)	10 693 (14)
Current tobacco use	4029 (29)	8116 (26)	4974 (23)	1755 (22)	643 (23)	19 517 (25)
Current alcohol use	9645 (70)	22 549 (71)	15 326 (70)	5502 (70)	1991 (71)	55 013 (70)
Any regular leisure-time physical activity	3379 (24)	6760 (21)	3429 (16)	1028 (13)	321 (11)	14 917 (19)
Mean physical measurements (SD)						
Height, *cm*	153 (7)	152 (6)	151 (6)	151 (6)	151 (6)	152 (6)
Weight, *kg*	54 (6)	64 (6)	74 (7)	84 (8)	99 (11)	68 (12)
BMI, *kg/m²*	23.1 (1.5)	27.6 (1.4)	32.1 (1.4)	37.0 (1.4)	43.4 (3.3)	29.6 (5.1)
Waist circumference, *cm*	80 (7)	89 (7)	98 (7)	107 (8)	117 (10)	93 (12)
Hip circumference, *cm*	95 (6)	102 (6)	111 (7)	120 (8)	132 (11)	106 (11)
Waist-to-hip ratio	0.84 (0.06)	0.87 (0.06)	0.88 (0.06)	0.89 (0.06)	0.89 (0.07)	0.87 (0.06)
Waist-to-height ratio	0.52 (0.05)	0.58 (0.05)	0.65 (0.05)	0.71 (0.05)	0.78 (0.07)	0.61 (0.08)
SBP, *mm Hg*	119 (15)	123 (15)	127 (16)	130 (16)	134 (16)	125 (16)
DBP, *mm Hg*	78 (10)	81 (10)	83 (10)	86 (10)	88 (10)	82 (10)
HbA_{1c} level						
Mean (SD), *%*	5.3 (0.4)	5.4 (0.4)	5.6 (0.4)	5.7 (0.4)	5.8 (0.4)	5.5 (0.4)
6.5% to <7%, *n (%)*	53 (<0.5)	313 (1)	532 (2)	297 (4)	183 (7)	1378 (2)
Long-term medication use, *n (%)*						
Any antihypertensive	949 (7)	3395 (11)	3410 (16)	1561 (20)	768 (27)	10 083 (13)
Any antithrombotic	315 (2)	707 (2)	614 (3)	248 (3)	98 (3)	1982 (3)
Any lipid-lowering agent	59 (<0.5)	140 (<0.5)	83 (<0.5)	31 (<0.5)	8 (<0.5)	321 (<0.5)

cate according to the International Classification of Diseases, 10th Revision (12). Study clinicians reviewed and, if necessary, recoded the underlying cause of death (for example, accepting diabetes as the underlying cause only for deaths due to acute diabetic crises) (13).

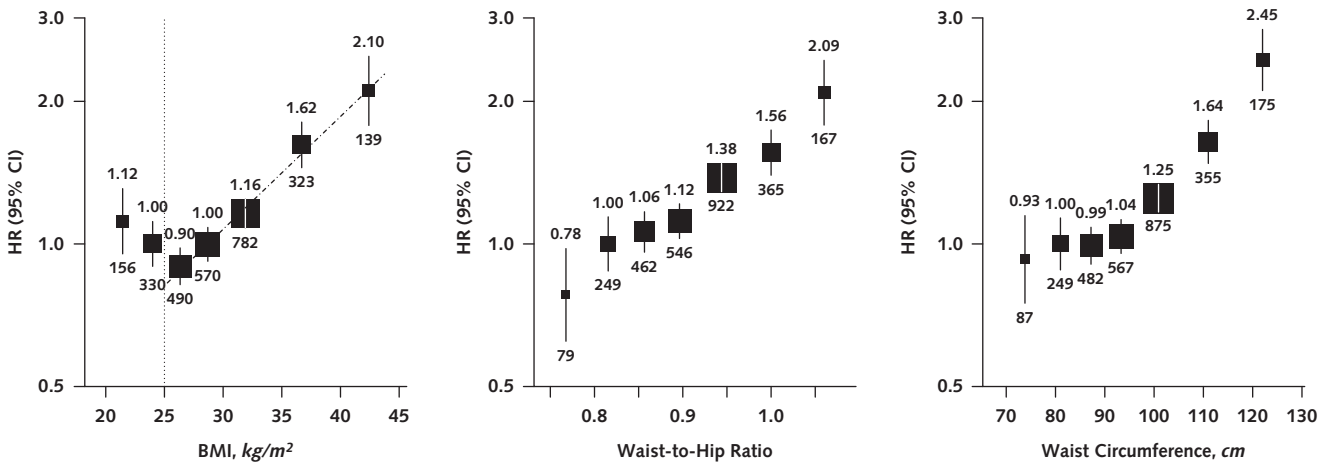
Statistical Analysis

The statistical methods are described in detail in the Supplement (available at Annals.org). Initially, BMI was grouped into 5 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 of 18.5 to 60 kg/m². However, because nearly two thirds of the cohort was classified as normal or overweight, these 2 categories were subdivided, yielding 7 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 BMI analyses, waist-to-hip ratio and 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.

To limit the effects of reverse causality, the main analyses excluded participants with certain previous diseases and those who died within 5 years of recruitment. For these analyses, the remaining deaths and follow-up were divided into 5-year "age-at-risk" ranges, that is, the age ranges in which those deaths occurred during follow-up. The main analyses included deaths that occurred at ages 40 to <75 years (defined as "premature" deaths). A secondary analysis was of deaths that occurred at ages 75 to <90 years.

Cox regression, stratified by 5-year age-at-risk groups, was used to assess the relevance of BMI, waist-to-hip ratio, and waist circumference (in each of the 7 groups described earlier) to mortality. The hazard ratio (HR) was estimated for each exposure group after 1 of these groups was designated as the reference, with an HR of 1. The variance of the log risk in each group, including the reference, 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 (for example, on their 75th birthday for analyses of deaths occurring at ages 40 to <75 years) or at the end of follow-up (1 January 2016). In analyses of cause-specific mortality (Supplement Table 1, available at Annals.org), participants whose cause of death differed from the one being analyzed were censored at their date of death. All Cox regression analyses were adjusted for sex, district of residence (1 of 2 districts), self-reported highest education level attained (university or college, high school, elementary school, other), leisure-

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



Analyses excluded participants with an HbA_{1c} level of ≥7% at recruitment, those with diabetes or other chronic diseases (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema), and all deaths in the first 5 years of follow-up. The HRs for the 7 BMI categories—18.5 to <22.5 kg/m^2, 22.5 to <25 kg/m^2 (the reference group), 25 to <27.5 kg/m^2, 27.5 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, and 40 to 60 kg/m^2—are plotted against the mean BMI in each group. For waist-to-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% CIs, with the area of each square proportional to the amount of statistical information. For each group, the HR is above the square and the number of deaths is below. The dashed diagonal line (left) represents the line of best fit above a BMI of 25 kg/m^2 and corresponds to an HR of 1.30 (95% CI, 1.24–1.36) per 5-kg/m^2 increase in BMI. Hazard ratio estimates are stratified by age at risk (in 5-year ranges) and are adjusted for sex, district of residence, highest education level attained, leisure-time physical activity, smoking status, and alcohol intake. BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio.

time physical activity (none, up to twice weekly, at least 3 times weekly), smoking status (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 included BMI as a continuous variable, with HRs estimated for 5-kg/m^2 increases in BMI. With the same adjustment for covariates as described earlier, these HRs were estimated separately for participants with a BMI <25 kg/m^2 and those with a BMI of 25 kg/m^2 or greater. All-cause mortality HRs associated with BMI also were estimated separately for deaths occurring 5 to <10 years and those occurring 10 years or more after recruitment. Other sensitivity analyses involved the following: exclusion of current or former smokers, exclusion of anyone with an HbA_{1c} concentration of 6.5% to <7%, inclusion of those with previously diagnosed diabetes but good glycemic control (defined as an HbA_{1c} level <7%), and fitting the household of each participant as a random effect (to allow for any clustering).

Analyses were performed with SAS, version 9.4 (SAS Institute); Stata, version 13.1 (StataCorp); and R, version 3.5.3 (R Project for Statistical Computing; www.r-project.org).

Study Oversight

Research ethics approval was obtained from the Mexican Health Ministry, Mexican National Council of Science and Technology, and University of Oxford (United Kingdom). All participants provided written informed consent.

Role of the Funding Source

The funding sources had no role in the design, conduct, or analysis of the study or the 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 or older at recruitment or had a history of chronic disease other than diabetes. Another 4795 participants were excluded because they had extreme, uncertain, or missing exposure; covariate; or mortality outcome data (including 623 with a BMI <18.5 kg/m^2 and 30 with a BMI >60 kg/m^2). The remaining 146 053 participants included 19 068 with previously diagnosed diabetes and 4888 others with an HbA_{1c} concentration of 7% or higher at recruitment. Both groups were excluded from the main analyses, leaving 122 097 participants: 115 400 aged 35 to <75 years and 6697 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 kg/m^2 (SD, 4.1 kg/m^2) in men and 29.6 kg/m^2 (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 blood pressure and HbA_{1c} levels. The proportion of participants with an HbA_{1c} concentration between 6.5% and 7% in-

creased from 1% in the lowest-BMI group (18.5 to <25 kg/m^2) to 7% in the highest-BMI group (40 to 60 kg/m^2). Similar patterns were observed for groups defined by waist-to-hip ratio or waist circumference (**Supplement Tables 2** and **3**, available at Annals.org). Body mass index was highly correlated with waist circumference (age-adjusted r = 0.83 in both men and women) but less strongly correlated with waist-to-hip ratio (r = 0.45 in men and 0.23 in women).

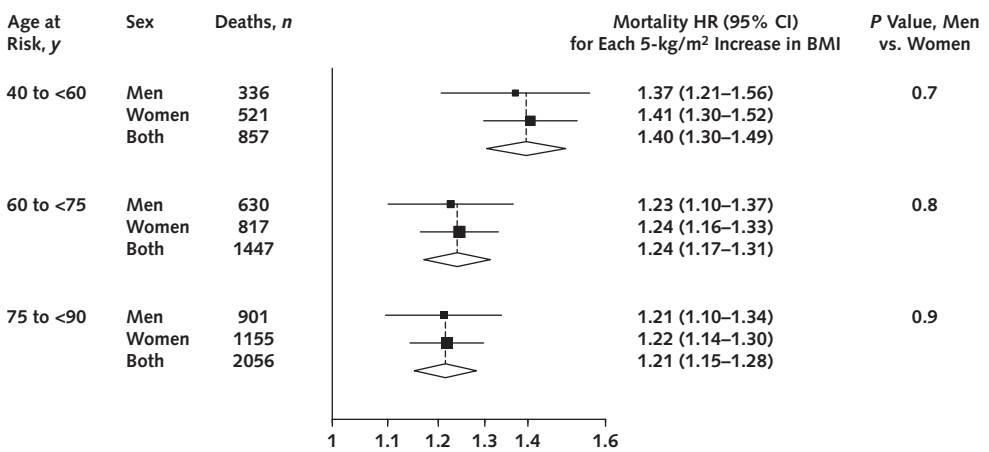
Adiposity and All-Cause Mortality

Figure 1 shows the associations between BMI, waist-to-hip ratio, and waist circumference and 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 7 baseline groups defined by BMI—18.5 to <22.5 kg/m^2, 22.5 to <25 kg/m^2 (reference), 25 to <27.5 kg/m^2, 27.5 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, and 40 to 60 kg/m^2—the HRs (and group-specific 95% CIs) were 1.12 (95% 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), respectively. Thus, BMI seemed to be inversely related to mortality below 25 kg/m^2, although this observation was based on only 486 deaths. Above 25 kg/m^2, however, 2304 deaths occurred, the BMI range was wider, and BMI had a highly significant positive relationship to all-cause mortality, with each 5-kg/m^2 increase associated with 30% higher mortality (HR, 1.30 [CI, 1.24 to 1.36]). In comparison, the relationship between waist-to-hip ratio and all-cause mortality seemed to be continuous and approximately "log-linear" throughout the range studied. Finally, the relationship between waist circumference and all-cause mortality seemed to be curvilinear.

Figure 2 shows that the positive association of BMI with all-cause mortality among participants with a BMI above 25 kg/m^2 was stronger at younger than older ages, with each 5-kg/m^2 increase in BMI associated with a mortality increase of 40% at ages 40 to <60 years (HR, 1.40 [CI, 1.30 to 1.49]), 24% at ages 60 to <75 years (HR, 1.24 [CI, 1.17 to 1.31]), and 21% at ages 75 to <90 years (HR, 1.21 [CI, 1.15 to 1.28]) (P for effect modification across the 3 age ranges = 0.003). Within each age range, however, the associations between BMI and all-cause mortality were similar in men and women and were not materially affected by district, smoking status, education level, physical activity, or alcohol intake (**Supplement Figure 1**, available at Annals.org). When the positive association of BMI with mortality at ages 40 to <75 years was subdivided by length of follow-up, it seemed to be stronger for deaths occurring 10 years or more after recruitment (HR, 1.37 [CI, 1.28 to 1.46]) than those occurring 5 to <10 years after recruitment (HR, 1.24 [CI, 1.17 to 1.32]).

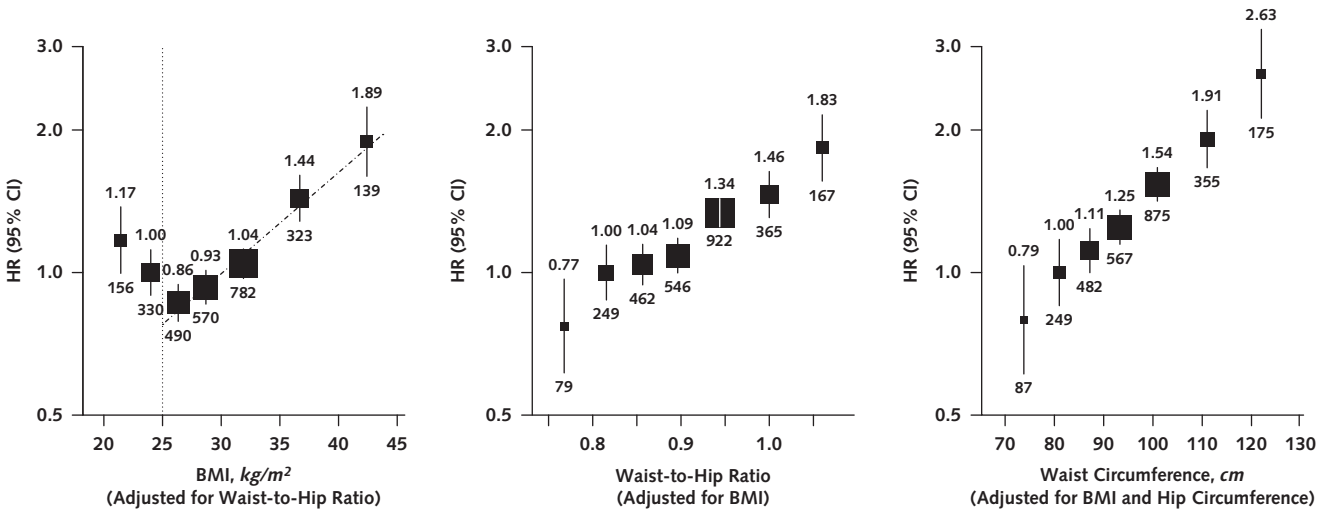
Figure 3 explores the independent relevance of the 3 markers of adiposity to mortality at ages 40 to <75 years. Because BMI and waist-to-hip ratio were somewhat correlated, adjustment for either of these 2 measures reduced the other's association with all-cause mortality; however, in both cases, strong relationships remained. Because 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.

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.



Analyses excluded participants with an HbA_{1c} level ≥7% at recruitment, those with diabetes or other chronic diseases (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema), and all deaths in the first 5 years of follow-up. All analyses included participants aged 35 to <75 years at recruitment, except for analyses of deaths occurring from 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 were stratified by age at risk (in 5-year ranges) and adjusted for district of residence, highest education level attained, leisure-time physical activity, smoking status, and alcohol intake. The overall HR estimates also were adjusted for sex. A test for trend in the log HR across the 3 age-at-risk categories shown yielded a χ^2 statistic of 8.9 (P = 0.003). BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio.

Figure 3. Effects of further adjustment for other markers of adiposity on the relevance of BMI, waist-to-hip ratio, and waist circumference to all-cause mortality at ages 40 to <75 years.



Analyses excluded participants with an HbA_{1c} level of ≥7% at recruitment, those with 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 HRs for the 7 BMI categories–18.5 to <22.5 kg/m^2, 22.5 to <25 kg/m^2 (the reference group), 25 to <27.5 kg/m^2, 27.5 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, and 40 to 60 kg/m^2–are plotted against the mean BMI in each group. For waist-to-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% CIs, with the area of each square proportional to the amount of statistical information. For each group, the HR is above the square and the number of deaths is below. The dashed diagonal line (left) represents the line of best fit above a BMI of 25 kg/m^2 and corresponds to an HR of 1.27 (95% CI, 1.21–1.32) per 5-kg/m^2 increase in BMI. Hazard ratio estimates are stratified by age at risk (in 5-year ranges) and are adjusted for sex, district of residence, highest education level attained, leisure-time physical activity, smoking status, and alcohol intake. In addition, the BMI results were adjusted for waist-to-hip ratio (*left*), the waist-to-hip ratio results were adjusted for BMI (*middle*), and the waist circumference results were adjusted for hip circumference and BMI (*right*) (with adjustments based on the aforementioned 7 BMI categories). BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio.

Table 2. BMI and Cause-Specific Mortality at Ages 40 to <75 Years*

Cause of Death	BMI 18.5 to <25 kg/m² (*n* = 22 177)		BMI 25 to 60 kg/m² (*n* = 93 223)	
	Deaths, *n*	HR per 5 kg/m² (95% CI)	Deaths, *n*	HR per 5 kg/m² (95% CI)
Vascular				
Cardiac	88	0.97 (0.48–1.95)	418	1.35 (1.22–1.50)
Stroke	25	0.56 (0.16–1.95)	165	1.25 (1.06–1.47)
Other	15	3.17 (0.45–22.21)	53	2.06 (1.67–2.55)
Subtotal: vascular	128	0.98 (0.55–1.76)	636	1.39 (1.28–1.51)
Metabolic				
Renal/acute diabetic crisis	24	0.36 (0.11–1.21)	188	1.52 (1.33–1.74)
Hepatobiliary	50	1.25 (0.47–3.30)	258	1.33 (1.16–1.51)
Subtotal: any vascular or metabolic	202	0.91 (0.57–1.43)	1082	1.40 (1.32–1.49)
Other				
Neoplastic	136	0.81 (0.47–1.41)	631	1.10 (1.01–1.21)
Respiratory	58	0.54 (0.24–1.20)	236	1.42 (1.25–1.61)
Infective	30	0.92 (0.28–3.04)	163	1.43 (1.23–1.67)
Other/ill-defined/external	60	0.52 (0.24–1.15)	192	1.12 (0.94–1.32)
Total: all causes	486	0.77 (0.57–1.02)	2304	1.30 (1.24–1.36)†

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio.
* Analyses involved the 115 400 participants aged 35 to <75 years who did not have an HbA_{1c} level ≥7%, diabetes, or other chronic diseases (ischemic heart disease, stroke, chronic kidney disease, cirrhosis, cancer, or emphysema) at recruitment. However, because the analyses exclude the first 5 years of follow-up, they include only deaths at ages 40 to <75 years. HR estimates are adjusted for age at risk, sex, district of residence, self-reported highest education level attained, leisure-time physical activity, smoking status, and alcohol intake.
† Addition of a further quadratic term for BMI in this model did not significantly improve the model fit.

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 BMI increase separately for the ranges of 18.5 to <25 kg/m^2 and 25 to 60 kg/m^2 (for the shapes of these associations, see Supplement Figure 2 [available at Annals.org]). The numbers of deaths from particular causes among participants with a BMI of 18.5 to <25 kg/m^2 were too small for statistical stability; however, above this range, strong positive associations were observed for deaths due to vascular disease, renal disease or acute diabetic crisis, hepatobiliary disease, respiratory disease, and infection, although not those due to cancer or the composite of all other, ill-defined, or external causes. For the combination of death from any vascular or metabolic cause (that is, vascular, renal or acute diabetic, or hepatobiliary), each 5-kg/m^2 increase in BMI above 25 kg/m^2 was associated with a 40% increase in mortality (HR, 1.40 [CI, 1.32 to 1.49]).

Cause-specific HRs associated with BMI were consistent when analyses were restricted to never-smokers, excluded participants with an HbA_{1c} level of 6.5% to <7%, or included those with previously diagnosed diabetes but good glycemic control (defined as an HbA_{1c} level under 7%) (Supplement Table 4, available at Annals.org). Results were also virtually identical when analyses were repeated using a multilevel model with household fitted as a random effect to allow for any clustering (Supplement Table 5, available at Annals.org).

Reverse Causality

To help assess the causal effects of adiposity and limit the extent to which associations between baseline adiposity and mortality are distorted by any effects of diabetes or other diseases on the baseline measurements, the main analyses looked at deaths occurring more than 5 years after the baseline measurements and excluded participants with an HbA_{1c} level of 7% or greater, previously diagnosed diabetes, or other chronic diseases at recruitment. Supplement Figures 3 and 4 (available at Annals.org) show the substantial biases that would have resulted if such exclusions had not been implemented. For BMI and 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 (Supplement Figure 3). This would have been qualitatively different from the associations in the main analyses (Figure 1), because among participants who had an HbA_{1c} level of 7% or higher or diabetes at recruitment, a strong inverse association was found between BMI and all-cause mortality (Supplement Figure 4).

DISCUSSION

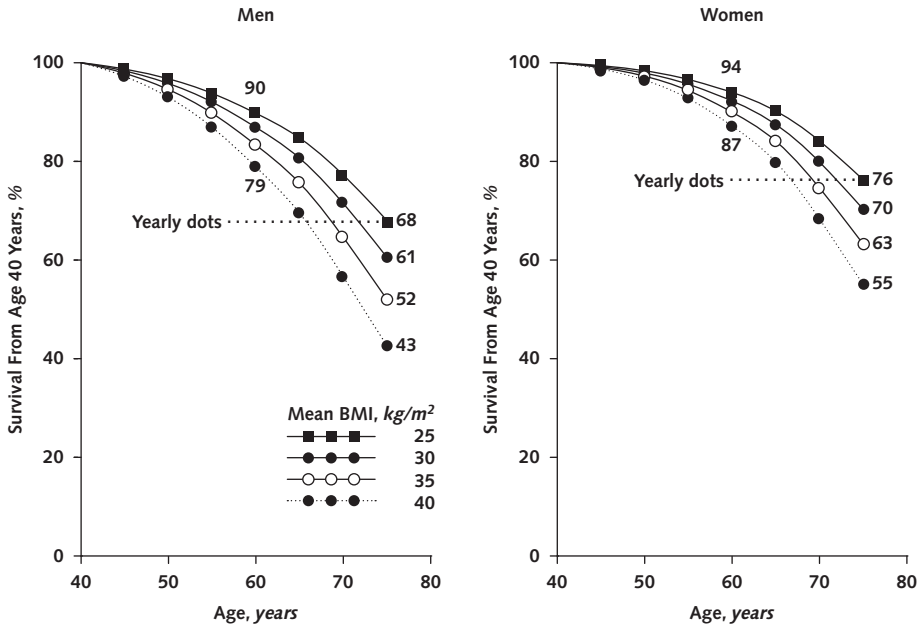
Both general and abdominal adiposity were strongly associated with all-cause mortality in this large study of Mexican adults. Each 5-kg/m^2 increase in BMI above 25 kg/m^2 was associated with a 30% increase in all-cause mortality. In this BMI range, the association with all-cause mortality was stronger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

A surprising finding, however, was that after adjustment for BMI and hip circumference, the association between low waist circumference and low mortality was strengthened, making the adjusted relationship of waist circumference to mortality approximately log-linear throughout its entire range. Therefore, although knowledge of height, weight, and hip circumference may 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 actual and predicted waist circumference remains strongly associated with mortality. This observation supports previous evidence that *central* adiposity is of particular importance (15).

Poorly controlled diabetes, which is common in Mexico (13, 16), may cause weight loss, resulting in a misleadingly inverse association between HbA_{1c} levels and BMI, and a misleadingly inverse association between BMI and mortality in adults with diabetes (Supplement Figure 4). To help avoid such associations, our analyses excluded participants who had an elevated HbA_{1c} level or diabetes at recruitment and those who died within 5 years, and sensitivity analyses illustrate the importance of these exclusions. The risks associated with overweight or obesity in our main analyses are therefore consistent with those found in appropriate analyses of other Western populations (3, 15, 17, 18). They differ substantially, however, from previous claims—based on analyses without the necessary exclusions—that overweight and obesity in Hispanic populations are not associated with higher risks for all-cause mortality (the so-called Hispanic paradox) (7, 8). This discrepancy may reflect the failure of previous analyses to control adequately for the extent to which diabetes or other disease processes may distort the relationship between BMI and mortality. They also differ from recent findings in a study of similar size and duration among U.S. women which reported that, for a given waist circumference, BMI appeared to be unrelated to mortality (19).

With direct rather than self-reported anthropometry, along with the aforementioned precautions against being substantially misled by reverse causality, this study could reliably assess the separate and joint associations between mortality and BMI, waist-to-hip ratio, and waist circumference. Although the study could not rule out some residual confounding and lacked other methods of assessing abdominal adiposity, its major 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 lipid levels, markers of renal function, or other biochemical markers). The study also had several limitations. First, data regarding the incidence of nonfatal diabetes and renal and vascular disease were lacking.

Figure 4. Hypothetical effect of a mortality HR of 1.30 per 5-kg/m^2 increase in BMI on survival from age 40 to 75 years, at 2016 mortality rates in Mexico.



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

Second, identification of causes of death relied on death certificates; however, the main analyses focused on all-cause mortality. Third, too few cancer deaths occurred to enable a reliable investigation of site-specific cancer. Finally, as in many prospective studies, participants were probably somewhat healthier than the general population, especially because the analyses excluded 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 for premature death. Figure 4 shows what our HR of 1.30 per 5-kg/m^2 BMI increase would imply for the dependence on BMI of the probability of survival from age 40 years if the 2016 Mexican national death rates corresponded to those observed in a population with a BMI of 29 kg/m^2. Compared with a BMI of 25 kg/m^2, adult life expectancy from age 40 years would be reduced by about 3 years at a BMI of 30 kg/m^2 but by nearly 10 years at a BMI of 40 kg/m^2.

Obesity is a leading cause of diabetes, and in Mexico diabetes is a major cause of premature death and disability, accounting for at least one third of deaths among persons aged 35 to 74 years (13). Although we assessed only mortality, our findings suggest that even a moderate population-wide reduction in average adiposity levels might substantially reduce both morbidity and mortality in middle age. In addition to their relevance to Mexico's population, these findings are likely to be relevant to other Hispanic groups, including millions of Mexican Americans (because they refute earlier suggestions of a Hispanic obesity paradox). However, 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 diseases.

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 similar to those observed in high-income populations. We also found that given BMI, the waist-to-hip ratio remains of substantial additional relevance to mortality, suggesting that central obesity is particularly harmful.

From University of Oxford, Oxford, United Kingdom (L.G., R.W., R.C., R.C., W.G.H., M.H., S.L., R.P., J.R.E.); National Autonomous University of Mexico, Mexico City, Mexico (J.A., R.R., R.T., A.G., C.G., M.S., P.K.); and Salvador Zubirán National Institute of Medical Sciences and Nutrition, Mexico City, Mexico (E.C.).

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Corresponding Authors: Jonathan R Emberson, PhD, MRC Population Health Research Unit, Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom; e-mail, jonathan.emberson@ndph.ox.ac.uk, and Jesus Alegre-Díaz, MD, Facultad de Medicina UNAM, Avenida Universidad 3000, Cd. Universitaria, 04510 Coyoacan, Mexico City, Mexico; e-mail, inypcjad@gmail.com.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Ms. Gnatiuc and Drs. Clarke, Collins, and Peto: Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom. Ms. Wade and Drs. Herrington, Hill, Lewington, and Emberson: MRC Population Health Research Unit, Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom.

Drs. Alegre-Díaz, Tapia-Conyer, and Kuri-Morales; Mr. Ramirez-Reyes; Mr. Garcilazo-Ávila; Mr. Gonzáles-Carballo; and Ms. Solano-Sanchez: Facultad de Medicina UNAM, Avenida Universidad 3000, Cd. Universitaria, 04510 Coyoacan, Mexico City, Mexico.

Dr. Chiquete: Salvador Zubirán National Institute of Medical Sciences and Nutrition, Vasco de Quiroga 15, Belisario Domínguez Secc 16, 14080 Mexico City, Mexico.

Author Contributions: Conception and design: L. Gnatiuc, J. Alegre-Díaz, R. Tapia-Conyer, R. Clarke, R. Peto, J.R. Emberson, P. Kuri-Morales.

Analysis and interpretation of the data: L. Gnatiuc, R. Wade, R. Clarke, R. Peto, J.R. Emberson.

Drafting of the article: L. Gnatiuc, J.R. Emberson.

Critical revision for important intellectual content: L. Gnatiuc, J. Alegre-Díaz, R. Wade, R. Ramirez-Reyes, R. Tapia-Conyer, A. Garcilazo-Ávila, E. Chiquete, C. Gonzáles-Carballo, M. Solano-Sanchez, R. Clarke, R. Collins, W.G. Herrington, M. Hill, S. Lewington, R. Peto, J.R. Emberson, P. Kuri-Morales.

Final approval of the article: L. Gnatiuc, J. Alegre-Díaz, R. Wade, R. Ramirez-Reyes, R. Tapia-Conyer, A. Garcilazo-Ávila, E. Chiquete, C. Gonzáles-Carballo, M. Solano-Sanchez, R. Clarke, R. Collins, W.G. Herrington, M. Hill, S. Lewington, R. Peto, J.R. Emberson, P. Kuri-Morales.

Statistical expertise: R. Wade, R. Peto, J.R. Emberson.

Obtaining of funding: J. Alegre-Díaz, R. Tapia-Conyer, R. Collins, R. Peto, J.R. Emberson, P. Kuri-Morales.

Administrative, technical, or logistic support: R. Ramirez-Reyes, M. Solano-Sanchez, M. Hill.

Collection and assembly of data: J. Alegre-Díaz, R. Ramirez-Reyes, R. Tapia-Conyer, W.G. Herrington, M. Hill, J.R. Emberson, P. Kuri-Morales.