Article

Validation of clinical and preclinical obesity across global cohorts

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In 2025, a *Lancet* Commission proposed distinguishing clinical obesity, defined by adiposity-related organ dysfunction, from preclinical obesity, defined by excess adiposity with preserved function, and recommended using anthropometric measures beyond body mass index (BMI) to confirm obesity status[1]. Here we report the comparative performance of this framework versus conventional BMI-based classification using prevalence, incidence and mortality data from 844,108 adults across four cohorts in China, the UK, the USA and Spain. Complementing BMI with waist circumference and waist-to-height ratio data showed that BMI alone overestimated obesity in 1.2–3.1% and underestimated it in 5.2–8.6% of participants across cohorts. The combined anthropometric definition increased overall obesity prevalence by 3.3–7.4% relative to BMI-based classification. Clinical obesity accounted for 22.7–31.3% of total obesity, with an overall population prevalence of 5.6–10.9%. A large proportion of individuals (between 77.4% and 91.3%) with preclinical obesity at baseline showed no progression to clinical obesity over 10 years. Increased mortality risk was associated with the combined anthropometric definition of obesity, but not with BMI-only obesity. Clinical obesity was associated with substantially higher all-cause mortality (hazard ratio 1.69, 95% confidence interval 1.64–1.73), whereas preclinical obesity conferred only modest risk (1.19, 1.14–1.24). These findings support the global adoption of the *Lancet* Commission diagnostic framework to improve obesity care and policy.

Medical diagnoses typically define disease on the basis of objective signs of organ dysfunction[2] (see https://www.merriam-webster.com/dictionary/diagnosis). By contrast, the health impact of obesity has historically been assessed using body mass index (BMI)—a proxy for body size—alongside obesity-related comorbidities[3–5]. This approach provides an aggregate measure of ill health rather than a disease-specific diagnosis.

The absence of a clinically grounded definition has impeded recognition of obesity as a distinct disease, contributing to gaps in care, inconsistent prevention, misallocated resources and persistent stigma[6,7].

To address this, in 2025, a *Lancet* Commission from *The Lancet Diabetes & Endocrinology* proposed a new diagnostic framework that distinguishes between two categories of obesity: clinical obesity, defined by excess adiposity impairing organ function or daily activities; and preclinical obesity, characterized by increased adiposity and increased health risks but with preserved organ and whole-body function[1]. The framework also recommends supplementing BMI with other anthropometric measures, such as waist circumference (WC), waist-to-height ratio (WHtR) or fat quantification with dual-energy X-ray absorptiometry, when available, to improve the detection of excess adiposity. Although consistent conceptually with diagnostic principles in medicine, the clinical implications of this framework remain uncertain. It is unknown how substantially the recommended use of additional anthropometric measures changes the classification of obesity compared with BMI alone, or whether the distinction between clinical and preclinical obesity captures meaningfully different health states. The natural history of preclinical obesity is also poorly characterized, including the extent to which it remains stable or progresses to clinical obesity over time. More broadly, whether these classifications show consistent associations with

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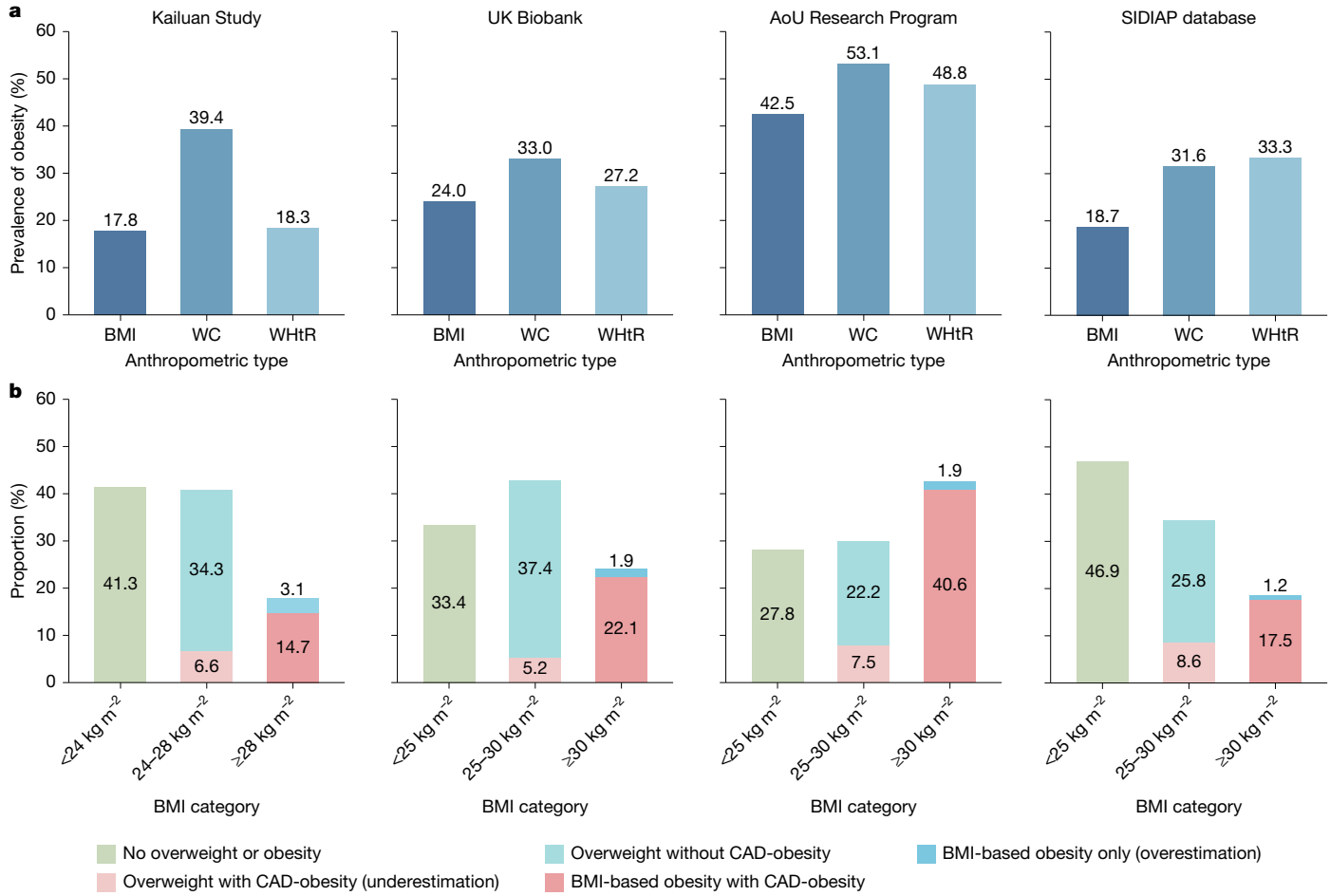


Fig. 1 | Prevalence and classification accuracy for BMI-based obesity versus CAD-obesity. Definitions of BMI-based obesity, WC-based obesity, WHtR-based obesity and CAD-obesity are provided in the Methods. The analyses included 137,795 participants from the Kailuan Study, 436,203 participants from the UK Biobank, 218,841 participants from the All of Us (AoU) Research Program and 51,269 participants from the SIDIAP database. Prevalence estimates are presented as percentages. **a**, Prevalence of obesity defined separately by BMI, WC and WHtR. **b**, Reclassification of obesity status across BMI-defined categories after applying CAD-obesity criteria. Colours indicate the corresponding reclassification categories as defined in the figure.

prognosis across populations and healthcare settings has yet to be established. We examined these questions using data from 844,108 adults from four large cohorts in China, the UK, the USA and Spain, aiming to evaluate the *Lancet* Commission's proposed diagnostic framework in terms of obesity classification, the distribution and longitudinal course of clinical and preclinical obesity and their associations with mortality.

Multi-anthropometric definition of obesity

To assess whether incorporating other anthropometric measures (WC and WHtR) improves obesity detection beyond the use of BMI alone, we analysed data from four cohorts: the Kailuan Study (China, n = 137,795), the UK Biobank (UKB, n = 436,203), the All of Us Research Program (AoU; USA, n = 218,841) and the SIDIAP database (Spain, n = 51,269). The characteristics of the study populations are shown in Supplementary Table 1, selection of study participants from each cohort is shown in Supplementary Figs. 1–4 and the details of study design of each cohort are presented in the Methods and Supplementary Methods. Following the *Lancet* Commission's proposed diagnostic criteria[1], obesity confirmation required any of the following three components: (1) BMI ≥ 40.0 kg m^{-2}; (2) BMI ≥ 30.0 kg m^{-2} (≥28.0 kg m^{-2} for Chinese individuals) plus elevated WC or elevated WHtR; or (3) BMI 25.0–29.9 kg m^{-2} (24.0–27.9 kg m^{-2} for Chinese individuals) plus both elevated WC and elevated WHtR. Elevated WC was defined as ≥102 cm for male and ≥88 cm for female individuals (≥90/85 cm (male/female) for Chinese individuals)[8,9], and WHtR thresholds varied by ethnicity (non-Hispanic white: male/female ≥0.57/0.58; non-Hispanic Black: ≥0.55/0.57; Hispanic: ≥0.57/0.59; Asian: ≥0.56/0.59; others: ≥0.50)[10].

Classification based on BMI alone resulted in both over- and under-identification of obesity across all four cohorts (Fig. 1 and Extended Data Table 1). The proportions classified as obese by BMI but without elevated WC or WHtR were 3.1% in the Kailuan Study, 1.9% in the UKB, 1.9% in the AoU and 1.2% in the SIDIAP, whereas 6.6%, 5.2%, 7.5% and 8.6%, respectively, of individuals with BMI-defined overweight met both WC and WHtR criteria for obesity-level adiposity. With the *Lancet* Commission's recommended multi-criteria definition, hereafter referred to as the combined anthropometric definition of obesity (CAD-obesity), overall obesity prevalence increased from 17.8% to 21.3% in the Kailuan Study, 24.0% to 27.3% in the UKB, 42.5% to 48.1% in the AoU and 18.7% to 26.1% in the SIDIAP. Overall, CAD-obesity yielded a modest net increase in obesity prevalence of 3.5% in China, 3.3% in the UK, 5.6% in the USA and 7.4% in Spain.

Clinical and preclinical categories

Clinical obesity was defined as CAD-obesity accompanied by at least one of the 18 adult diagnostic criteria specified by the *Lancet* Commission. These criteria represent obesity-related organ dysfunction or functional impairment across several systems, including cardiovascular (for example, heart failure, atrial fibrillation, thromboembolic disease

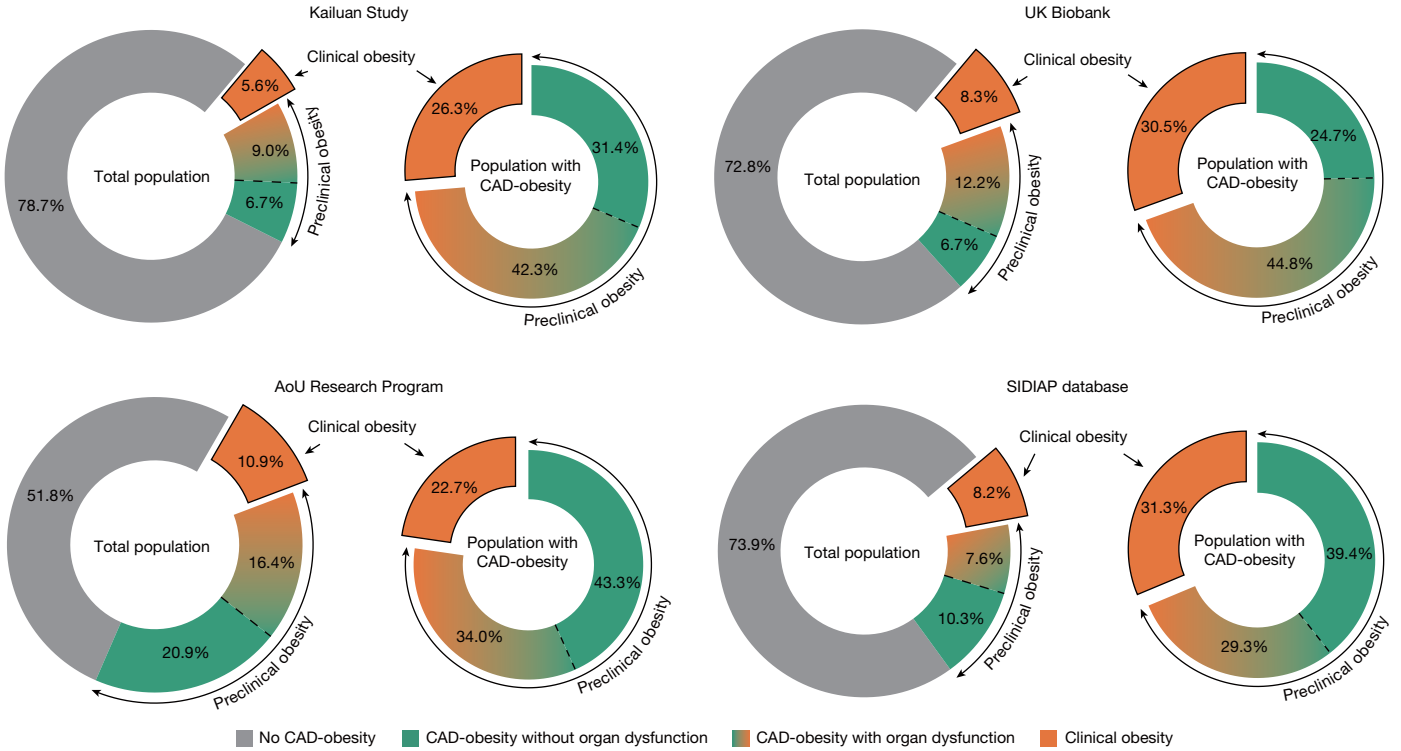


Fig. 2 | Prevalence of preclinical obesity and clinical obesity in all participants and in participants with CAD-obesity. Definitions of CAD-obesity, preclinical obesity and clinical obesity are provided in the Methods. The analyses included 137,795 participants from the Kailuan Study, 436,203 participants from the UK Biobank, 218,841 participants from the All of Us Research Program and 51,269 participants from the SIDIAP database. Grey segments represent individuals without CAD-obesity. Orange segments represent the estimated AF-adjusted prevalence component of clinical obesity, corresponding to CAD-obesity with organ dysfunction statistically attributable to CAD-obesity at the population level. Green segments represent individuals with CAD-obesity but without evidence of organ dysfunction. Segments with a colour gradient represent the estimated non-attributable prevalence component among participants with CAD-obesity and organ dysfunction after application of the AF adjustment. Together, the green and gradient segments represent the estimated AF-adjusted prevalence of preclinical obesity.

and hypertension), respiratory (obstructive sleep apnoea and chronic obstructive pulmonary disease), metabolic (combined dysglycaemia and dyslipidaemia), hepatic (MASLD with fibrosis), renal (chronic kidney disease), neurological (intracranial hypertension), musculoskeletal (hip or knee osteoarthritis), reproductive (infertility), urological (urinary incontinence) and lymphatic dysfunctions, together with limitations in daily activities. Criteria for clinical obesity were operationalized using predefined clinical, laboratory, imaging or diagnostic criteria adapted to the variables available in each cohort. Detailed definitions and cohort-specific assessment methods are provided in the Supplementary Methods and Supplementary Table 2.

However, not all organ dysfunction that coexists with CAD-obesity can be assumed to be attributable to obesity. We therefore applied an attributable fraction (AF) approach to provide a population-level estimate of attribution and to adjust subsequent estimates accordingly[11]. The AF was calculated as: $AF = \frac{HR-1}{HR}$, where HR denotes the hazard ratio for the association between CAD-obesity and risk of incident organ dysfunction with adjustment for relevant confounders using Cox proportional hazards models. The cohort-specific HRs used to derive the AF estimates were 1.62 (95% confidence interval (CI), 1.58–1.66) in the Kailuan Study, 1.68 (1.64–1.72) in the UKB, 1.67 (1.61–1.73) in the AoU and 2.07 (1.97–2.18) in the SIDIAP (Extended Data Table 2), corresponding to AF values of 0.383, 0.405, 0.401 and 0.517, respectively.

Because the distinction between clinical and preclinical obesity depends on the presence of organ dysfunction among individuals with CAD-obesity, we first quantified the observed crude prevalence of organ dysfunction and then applied the cohort-specific AF estimates to account for the proportion plausibly attributable to obesity at the population level. The crude prevalence of organ dysfunction among people with CAD-obesity ranged from 56.7% in the AoU to 75.3% in the UKB (Fig. 2; Extended Data Table 3). AF-adjusted clinical obesity accounted for 26.3% (95% CI: 25.2–27.3) of total obesity in the Kailuan Study, 30.5% (29.4–31.6) in the UKB, 22.7% (21.5–24.0) in the AoU, and 31.3% (30.9–31.8) in the SIDIAP (Fig. 2; Extended Data Table 3). Accordingly, the proportion of individuals with CAD-obesity but without any detectable organ dysfunction—representing the minimum estimate of preclinical obesity—ranged from 24.7% in the UKB to 43.3% in the AoU, and the maximum estimate of preclinical obesity (1 minus the AF-adjusted prevalence of clinical obesity) ranged from 68.7% in the SIDIAP to 77.3% in the AoU (Extended Data Table 3).

The overall prevalence of AF-adjusted clinical obesity in the full population was 5.6% (95% CI: 5.4–5.8) in the Kailuan Study, 8.3% (8.0–8.6) in the UKB, 10.9% (10.4–11.5) in the AoU and 8.2% (8.1–8.3) in the SIDIAP (Fig. 2 and Extended Data Table 3).

Sensitivity analyses restricting to the nine organ dysfunction indicators available across all datasets yielded results that were highly consistent with the primary analyses. Prevalence estimates changed minimally under the restricted definition, indicating that additional cohort-specific indicators contributed little to classification (Supplementary Tables 3 and 4). Indicators that were not universally available were individually rare, and most participants presenting them also had at least one of the nine common indicators, supporting the robustness and comparability of the classification across cohorts (Supplementary Table 5).

Ten-year stability of preclinical obesity

To assess the progression from preclinical to clinical obesity, we performed an analysis among individuals with CAD-obesity but without

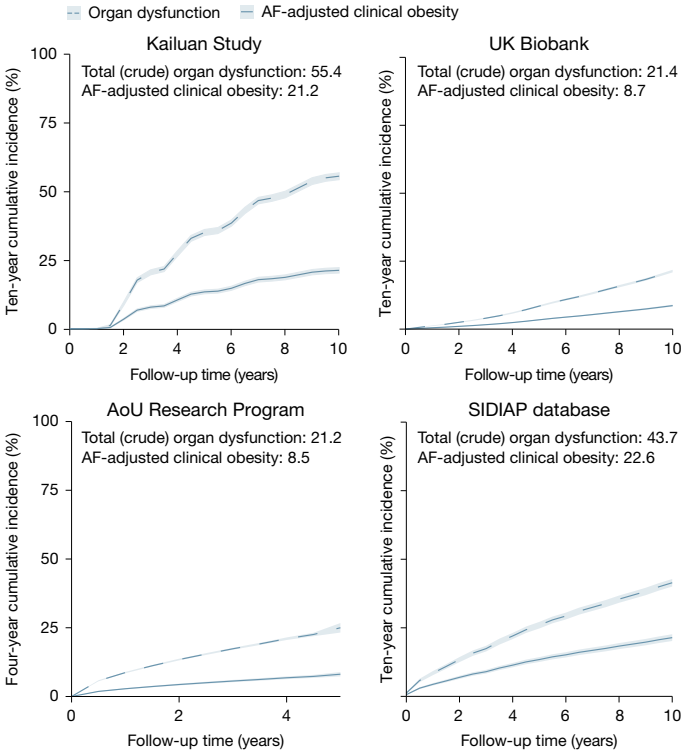


Fig. 3 | Cumulative incidence of organ dysfunction and AF-adjusted clinical obesity among individuals with preclinical obesity at baseline. The analyses included 8,009 participants from the Kailuan Study, 29,338 participants from the UK Biobank, 54,535 participants from the All of Us Research Program and 5,273 participants from the SIDIAP database, all of whom had preclinical obesity at baseline. Solid lines represent the estimated cumulative incidence of clinical obesity, calculated by applying AF-based estimates to the observed incidence of organ dysfunction among individuals with preclinical obesity. Dashed lines represent the observed cumulative incidence of incident organ dysfunction. Shaded areas represent the corresponding 95% CIs. Cumulative incidence curves were estimated using Kaplan–Meier methods and were generated from baseline until incident organ dysfunction, death or the end of follow-up, whichever occurred first. AF estimates were calculated from HRs derived using Cox proportional hazards models adjusted for cohort-specific covariates, as described in the Supplementary Methods.

any organ dysfunction at baseline. The AF-adjusted 10-year incidence of clinical obesity was 21.2% in the Kailuan Study, 8.7% in the UKB and 22.6% in the SIDIAP; because of a shorter follow-up in the AoU cohort, only an AF-adjusted 4-year incidence was calculated and an incidence of 8.5% was found (Fig. 3). Thus, approximately 70–90% of individuals with preclinical obesity remained stable over a decade. The incidence rates were similar between male and female individuals (Supplementary Fig. 5), and sensitivity analysis restricting to the nine organ dysfunction indicators yielded similar results (Kailuan Study: 21.4%; UK Biobank: 8.8%).

No excess mortality with BMI alone

Cox proportional hazards models were used to assess associations of BMI-based obesity and CAD-obesity with all-cause mortality, adjusting for sociodemographic covariates. The AoU cohort was excluded because of limited follow-up. Median follow-up was 15.3 years in the Kailuan Study (17,642 deaths), 13.8 years in the UKB (31,812 deaths) and 11.2 years in the SIDIAP (2,338 deaths).

Compared with individuals with no overweight or obesity, participants with BMI-defined overweight or obesity but without CAD-obesity had a lower all-cause mortality risk (pooled HR 0.88 [95% CI: 0.86–0.90] and 0.93 [0.86–0.99], respectively). By contrast, individuals with CAD-obesity, regardless of whether their BMI was in the overweight or obese range, had a significantly higher, albeit modest, mortality risk (pooled HR 1.06 [1.03–1.10] and 1.07 [1.05–1.10], respectively; Fig. 4a and Extended Data Table 4).

Further cause-specific mortality analyses were done in the UK Biobank (the only cohort with available cause-specific mortality data), including cardiovascular mortality, obesity-related cancer mortality and their combination (Supplementary Table 6). After multivariable adjustment, BMI-defined overweight or obesity without CAD-obesity was not associated with increased risks of these cause-specific mortality outcomes. By contrast, CAD-obesity was associated with higher risks, including among individuals in the BMI-defined overweight range.

In further sensitivity analyses, exclusion of deaths occurring within the first 5 years of follow-up did not materially alter the associations, arguing against reverse causation as a major explanation for the findings (Supplementary Table 7). The proportion of missingness was low across all cohorts, with no variable exceeding 20% (Supplementary Table 8), and a sensitivity analysis restricted to participants without missing variables also yielded robust results (Supplementary Table 9). Stratified analyses by smoking status confirmed that smoking was a strong effect modifier; however, among never-smokers, CAD-obesity remained consistently associated with higher mortality risk, whereas BMI-defined overweight and obesity in the absence of CAD-obesity showed no or modest mortality risk after multivariable adjustment (Supplementary Table 10).

Higher mortality in clinical obesity

We evaluated the association between clinical obesity and mortality risk. Participants were first categorized into four baseline groups: (1) no CAD-obesity and no organ dysfunction (reference group); (2) no CAD-obesity with organ dysfunction; (3) CAD-obesity without organ dysfunction (preclinical obesity); and (4) CAD-obesity with organ dysfunction (clinical obesity). Clinical obesity was associated with a substantially higher mortality risk (pooled HR, 1.69; 95% CI, 1.64–1.73), whereas preclinical obesity showed a modest association (pooled HR, 1.19; 95% CI, 1.14–1.24; Fig. 4b and Extended Data Table 5). Cohort-specific estimates were directionally consistent.

Sensitivity analyses by excluding deaths occurring within the first 2 or 5 years of follow-up or by incorporating waist-to-hip ratio into the diagnostic indicators did not materially alter the associations (Extended Data Table 6). The association between clinical obesity and mortality was stronger in female individuals and in those aged younger than 60 years ($P < 0.001$ for interactions; Extended Data Fig. 1 and Supplementary Table 11). In the age-stratified analysis, sensitivity analyses by further excluding deaths occurring within the first 5 years or restricting participants without missing variables yielded similar results to those of the primary analysis (Supplementary Tables 12 and 13), providing further reassurance against reverse causation and selection biases.

To disentangle the relative contributions of BMI-defined obesity, CAD-obesity and organ dysfunction to mortality risk, participants were further classified into eight groups according to the presence or absence of each component. In groups defined by organ dysfunction and CAD-obesity, BMI-defined obesity conferred little additional risk, when compared with the BMI-defined non-obese status. On the other hand, CAD-obesity showed a consistently higher mortality risk, and the highest mortality risks were observed among participants with both CAD-obesity and organ dysfunction (that is, clinical obesity) (Extended Data Table 7).

Separate cause-specific mortality analyses of clinical and preclinical obesity in the UK Biobank dataset showed that clinical obesity was consistently associated with substantially higher risks, with effect sizes generally stronger than those observed for all-cause mortality, whereas preclinical obesity showed elevated but consistently lower risks (Supplementary Table 14).

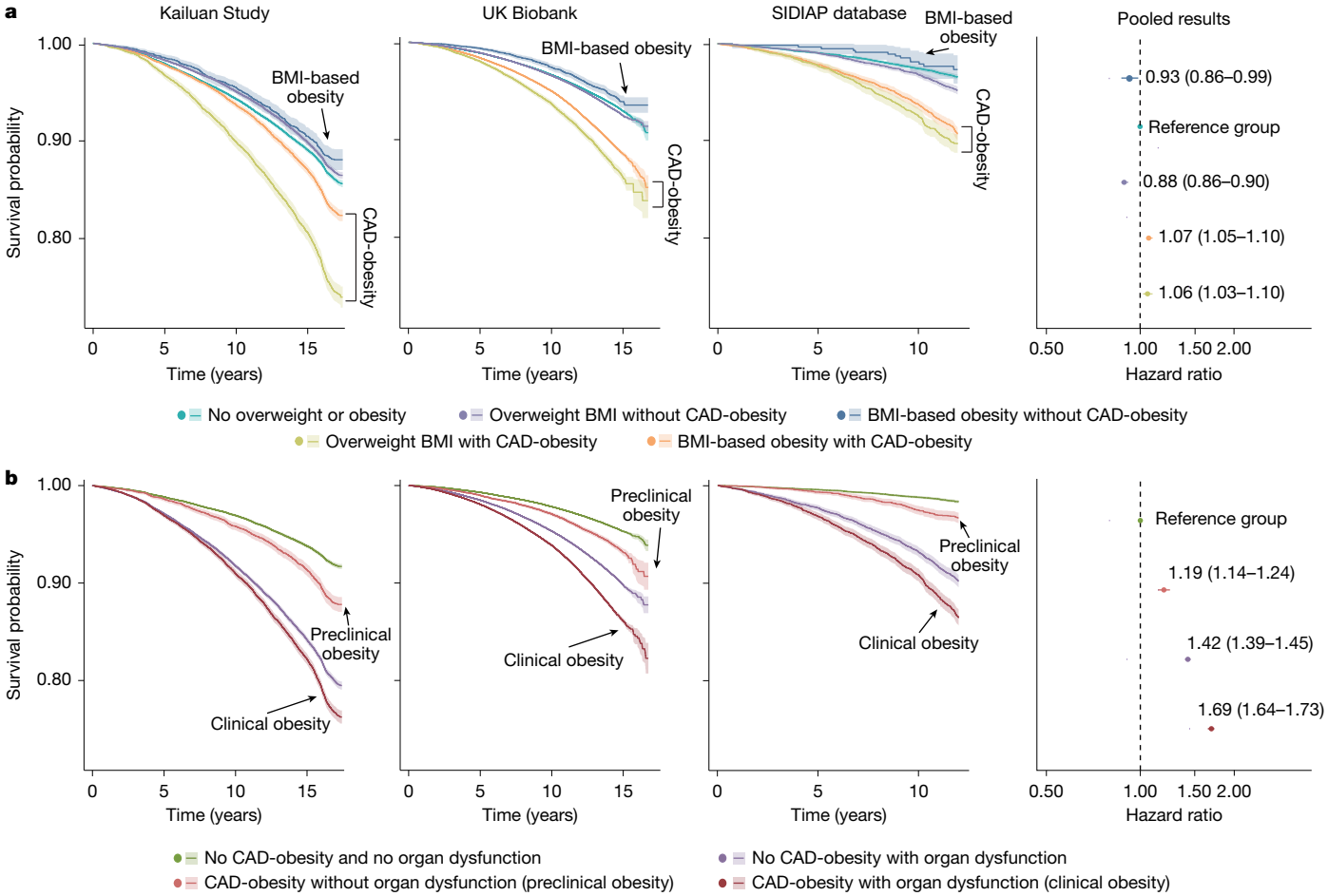


Fig. 4 | Cumulative survival and hazard ratios of mortality by BMI-based obesity, CAD-obesity and clinical obesity status. The analyses included 137,792 participants from the Kailuan Study, 436,203 participants from the UK Biobank and 51,269 participants from the SIDIAP database. Each panel presents Kaplan–Meier survival curves and adjusted HRs with 95% CIs for all-cause mortality, with cohort-specific survival curves shown on the left and pooled HR estimates from Cox proportional hazards models shown on the right. Solid lines in Kaplan–Meier plots represent survival probability estimates for each obesity classification group, with colours indicating the categories defined in each panel. Shaded areas around survival curves indicate 95% CIs. In forest plots, points represent HR point estimates and horizontal lines represent corresponding 95% CIs. The *x* axes of the forest plots are presented on a logarithmic scale. Cox proportional hazards models were adjusted for cohort-specific covariates as specified in the Supplementary Methods, and pooled HR estimates were obtained using fixed-effects models. All statistical tests were two-sided, and no adjustment for multiple comparisons was performed. **a**, Mortality risk according to BMI-based overweight or obesity and CAD-obesity status. Colours indicate BMI-based categories combined with CAD-obesity status: no overweight or obesity; overweight BMI without CAD-obesity; BMI-based obesity without CAD-obesity; overweight BMI with CAD-obesity; and BMI-based obesity with CAD-obesity. **b**, Mortality risk according to obesity stage defined by CAD-obesity and organ dysfunction, including preclinical and clinical obesity. Colours indicate four groups: no CAD-obesity and no organ dysfunction; no CAD-obesity with organ dysfunction; CAD-obesity without organ dysfunction (preclinical obesity); and CAD-obesity with organ dysfunction (clinical obesity).

Internal evaluation of WHtR cut-offs

We performed further complementary analyses to examine the appropriateness of the ethnicity-specific WHtR thresholds used to confirm obesity status. First, the relationship between BMI and WHtR was broadly consistent across cohorts (Pearson $r \geq 0.64$; Extended Data Fig. 2). On the basis of fitted linear regression models, the conventional WHtR cut-off of 0.50 corresponded approximately to the BMI-defined overweight threshold, whereas WHtR values corresponding to the BMI-defined obesity threshold were generally higher than 0.55 (from 0.55 to 0.60 across the four cohorts).

Mortality analyses showed a similar pattern. Restricted cubic spline models indicated that mortality risk began to increase at WHtR values around 0.55 (Extended Data Fig. 3). Consistently, participants with a WHtR between 0.50 and the ethnicity-specific thresholds had no excess mortality risk (pooled HR, 0.99; 95% CI, 0.97–1.02), whereas those with a WHtR above the ethnicity-specific threshold had a higher risk (pooled HR, 1.21; 95% CI, 1.18–1.24; Supplementary Table 15).

Using 0.50 instead of the ethnicity-specific thresholds substantially increased the proportion of participants defined as having obesity by meeting the WHtR criterion across all four cohorts (Kailuan, 59.2% versus 18.3%; UKB, 66.7% versus 27.2%; AoU, 74.3% versus 48.8%; SIDIAP, 71.1% versus 33.3%). When these thresholds were incorporated into the definition of confirmed obesity, the same risk pattern was observed: participants classified only by the 0.50 threshold showed no excess mortality (pooled HR, 1.00; 95% CI, 0.96–1.03), whereas those meeting the ethnicity-specific thresholds had a higher mortality risk (pooled HR, 1.20; 95% CI, 1.18–1.22; Supplementary Table 16).

Discussion

To our knowledge, this is the first large-scale, multinational study to comprehensively evaluate the *Lancet* Commission diagnostic

framework[1] against the widely used BMI-based classification. Previous studies have examined individual components of the framework—such as expanded anthropometric criteria or prevalence estimates of clinical obesity—but have lacked integrated assessment or longitudinal follow-up[12–16]. This study evaluated several interrelated elements of the new diagnostic framework: the implications of using combined anthropometric criteria to confirm obesity; their effects on prevalence and risk stratification compared with BMI alone; the importance of selecting appropriate anthropometric cut-offs; and the prognostic implications of distinguishing clinical from preclinical obesity.

With regard to anthropometric classification, our findings show that BMI alone both over- and under-identifies obesity and does not reliably distinguish individuals who have an increased mortality risk. These results support the Commission framework's use of complementary anthropometric measures alongside BMI to improve obesity classification and risk stratification. Although WC and WHtR are, like BMI, indirect measures of adiposity, increased values for these measures are (for anatomical and physiological reasons) more likely to reflect fat-mass expansion, whereas a higher BMI might also reflect greater lean mass. Their correlation with direct body-composition measurements[10] supports their use as a pragmatic means of detecting excess adiposity where direct measurement is impractical. Future studies should determine whether direct measurement of fat adds meaningful precision and could ultimately replace combined anthropometry if reliable bedside technologies become widely available.

We observed substantial discordance between BMI-based classification and CAD-obesity, with BMI overestimating obesity in 1.2–3.1% and underestimating it in 5.2–8.6% of participants across cohorts. When considered against national obesity estimates from the 2025 *World Obesity Atlas*[17], these proportions suggest that BMI misclassification affects tens of millions of individuals in countries with large populations, underscoring the potential public-health implications of seemingly modest differences in classification.

However, the effects of using a combined anthropometric definition of obesity depend, crucially, on how the Commission's recommendations are operationalized. Unlike our findings, previous studies in US cohorts reported that applying the *Lancet* Commission framework substantially increased overall obesity prevalence[12–16]. These discrepancies mainly reflect methodological differences, particularly the choice of anthropometric cut-offs and incomplete adherence to the framework's recommendations. In one study[14], higher prevalence estimates were driven by the use of a single low WHtR cut-off of 0.50 across populations, potentially classifying individuals with milder increases in adiposity and associated risk as having obesity. Another study[16] reported an overall obesity prevalence of 60% in the AoU cohort, compared with 48.1% in our analysis. In addition to using a single WHtR cut-off of 0.50, the study applied the cut-off across the full BMI range, including individuals with a normal BMI. This approach diverges from the Commission's recommendation that anthropometric confirmation be used mainly in individuals with BMI values below—but near —the BMI obesity threshold[1]. Applying anthropometric criteria outside this context risks classifying individuals with normal body weight and localized abdominal adiposity—such as those with lipodystrophy or related conditions, which are biologically and clinically distinct—as having obesity. For this reason, the Commission retained BMI as the initial screening tool[1], and we limited the assessment of obesity to participants within the conventional BMI-defined overweight and obesity ranges.

In closer alignment with the Commission's guidance, we applied obesity-level, ethnicity-specific thresholds for WC and WHtR. In our data, the conventional WHtR cut-off of 0.50 corresponded approximately to the BMI-defined overweight threshold, whereas WHtR values corresponding to the BMI-defined obesity threshold and increasing mortality risk were generally observed around or above 0.55. This convergence between anthropometric and mortality analyses supports the use of higher WHtR thresholds for obesity classification and is consistent with the previously proposed cut-off of 0.55–0.59 (ref. 10). Further prospective evaluation will be required to refine population-specific thresholds.

The application of obesity-level thresholds for WC and WHtR further illustrates the limitations of BMI-based classification. Although these measures remain indirect proxies of body fat, the reclassified groups had distinct mortality profiles, showing that conventional BMI categories encompass individuals with heterogeneous risk and that additional measures provide clinically relevant stratification beyond BMI alone. This is particularly consequential for the overweight category. The *Lancet* Commission framework intentionally does not retain overweight as a separate intermediate-risk category; instead, it extends the definition of obesity to individuals with a BMI classified as overweight who meet additional anthropometric criteria indicating obesity-level adiposity. Our data support this approach: individuals with a BMI in the overweight range who met CAD-obesity criteria had a mortality risk comparable with that of individuals with a BMI in the obesity range who also met CAD-obesity criteria. By contrast, those with a BMI classified as overweight who did not meet CAD-obesity criteria had no excess risk and, in several analyses, had a lower risk than did individuals with a normal BMI. The CAD-obesity criteria therefore identify adiposity-related risk that would otherwise remain obscured within the conventional overweight range.

The implications are substantial. An estimated 1.5 billion adults worldwide are classified as overweight by BMI[17], yet our findings indicate that individuals in this population should not all be regarded as being at increased risk. Our data suggest that combining BMI with WC and appropriately calibrated WHtR cut-offs, such as those evaluated here, can identify higher-risk individuals without substantially increasing overall obesity prevalence. This selective reclassification provides a clinically meaningful basis to inform individual care, health policy and resource allocation.

Anthropometric confirmation improves the identification of mortality risk associated with excess adiposity. However, because clinical obesity denotes an active disease state, its diagnosis requires a further step: establishing the presence of organ dysfunction that can plausibly be attributed to that adiposity. This requirement reflects a fundamental principle of disease definition: because similar alterations in organ function can arise from different disease processes, causality cannot be inferred from coexistence alone. For example, not all joint inflammation is caused by rheumatoid arthritis, nor is all heart failure attributable to the same underlying heart disease. In clinical practice, differential diagnosis addresses this uncertainty by considering alternative causes and, where possible, excluding them; it is therefore essential to diagnostic specificity. For this reason, organ dysfunction coexisting with obesity cannot automatically be considered obesity-related; doing so could overattribute dysfunction to obesity and substantially inflate estimates of clinical-obesity prevalence and incidence. Most previous applications of the framework classified all coexisting organ dysfunction as obesity-related without accounting for alternative causes[13–16], and might therefore have overestimated the prevalence of clinical obesity.

To mitigate this problem, we applied the AF method at the population level to estimate the proportion of organ dysfunction that is statistically attributable to CAD-obesity, and adjusted the prevalence and incidence estimates accordingly. Although this adjustment cannot establish causality in individual participants, it mitigates the risk of attributing organ dysfunction to obesity when other causes could be responsible, thereby reducing systematic overattribution and improving population-level estimates of the prevalence and incidence of clinical obesity. Notably, an earlier US study[12] using a different adjustment approach estimated the clinical-obesity prevalence as 9.7%, close to the 10.9% that was observed in the AoU cohort after AF adjustment. This concordance between studies using different population-level methods to account for plausible attribution provides some reassurance about the robustness of our estimates.

Our longitudinal and mortality analyses provide evidence supporting the distinction between clinical and preclinical obesity. Despite variation across cohorts, 70–90% of individuals with preclinical obesity did not progress to clinical obesity over 10 years. Clinical obesity was also associated with substantially higher all-cause and obesity-related mortality, whereas preclinical obesity showed only a modest excess mortality risk. The observed patterns of progression and differences in mortality risk show that these health states differ not only in their defining clinical characteristics but also in their prognostic implications. The distinct clinical and prognostic profiles of clinical and preclinical obesity provide a foundation for personalized, proportionate care. Preclinical obesity warrants a mostly preventive approach aimed at reducing future risk, with the nature and intensity of intervention guided by the individual's risk of progression and the presence of relevant comorbidities. By contrast, established functional impairment and higher mortality risk in clinical obesity justify greater urgency and, where appropriate, more intensive treatment and prioritized access. The distinction can therefore guide the purpose, timing and intensity of individual care and support evidence-based decisions on treatment prioritization, coverage and resource allocation.

Notably, using this distinction to guide proportionate care does not imply withholding treatment from people with preclinical obesity. One criticism of the *Lancet* Commission framework is that distinguishing preclinical from clinical obesity could encourage 'watchful waiting' or restrict access to treatment[18–20]. However, this concern seems to conflate diagnostic classification with treatment eligibility. Like any diagnosis, the distinction between clinical and preclinical obesity provides a snapshot of an individual's current health status; it does not prescribe inaction or determine eligibility for treatment by itself. Analogous distinctions—such as those between prediabetes and diabetes or adenomatous polyps and carcinoma—guide the purpose, urgency and intensity of intervention without precluding care for prediabetes or adenomatous polyps[21]. Accordingly, preclinical obesity might warrant active preventive treatment, including lifestyle, pharmacological or, in selected cases, surgical interventions, depending on progression risk and comorbidities that could benefit from weight reduction. Treatment decisions should therefore be informed by diagnosis but not reduced to diagnostic category alone.

Several limitations should be acknowledged. The retrospective design of our study and its reliance on electronic health record (EHR) data could limit diagnostic precision and introduce inter-cohort variability. Organ dysfunction was identified using administrative codes rather than standardized clinical assessments, and not all 18 dysfunction indicators were available in every cohort, potentially leading to the underestimation or misclassification of specific organ disease subtypes. This limitation is highlighted by the Kailuan cohort, in which the higher observed incidence of clinical obesity might reflect more frequent (biennial) clinical evaluations. However, sensitivity analyses showed that the additional indicators contributed minimally to classification, supporting the conclusion that differences in the number of available organ-dysfunction indicators are unlikely to be a major driver of the inter-cohort variability observed in the primary analyses. Finally, the AF method cannot determine attribution at the individual level, and future prospective studies using clinically adjudicated diagnoses of clinical and preclinical obesity will be essential to refine estimates of disease burden and progression. Nonetheless, the consistency of findings across geographically and demographically diverse cohorts strengthens the robustness, generalizability and clinical relevance of the proposed diagnostic framework.

In summary, BMI alone misclassifies obesity in a substantial proportion of individuals, both overestimating and underestimating the clinical relevance of excess adiposity, and does not meaningfully discriminate higher mortality risk. Integrating other anthropometric measures (such as WHtR and WC) and clinical criteria reflecting organ function into a multi-criteria framework improves obesity detection and aligns diagnosis more closely with true disease status. Clinical and preclinical obesity represent distinct and prevalent subgroups, with markedly different mortality risks. This study demonstrates the clinical utility and prognostic importance of distinguishing between clinical and preclinical obesity, and supports the global applicability of this classification scheme for guiding care and informing health policy.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-026-11237-5.

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Methods

Study population

This population-based multinational study analysed data from four large and well-characterized adult cohorts: the Kailuan Study (China), the UK Biobank (UKB; UK), the All of Us Research Program (AoU; USA), and the Information System for the Development of Research in Primary Care (SIDIAP, Spain). The Kailuan Study is an ongoing prospective cohort initiated between 2006 and 2007 among more than 100,000 employees of the Kailuan Group, with biennial follow-up examinations thereafter[22]. The UK Biobank enrolled around 500,000 individuals aged 37–73 years from 2006 to 2010 with questionnaires, physical examinations and biomarker assessments[23]. The All of Us Research Program is a US precision-medicine initiative aimed at building a diverse biomedical database to study the biological, clinical, social and environmental determinants of health[24]. The SIDIAP database includes pseudonymized EHRs from more than eight million individuals in Catalonia since 2006, with approximately 75% of the regional population represented[25].

The Kailuan Study was approved by the ethics committee of the Kailuan Medical Group. The UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee. The All of Us Research Program is overseen by the All of Us institutional review board. The SIDIAP analysis was approved by the IDIAP Jordi Gol ethics committee (20/204-P). All studies followed the Declaration of Helsinki, and all participants gave their written informed consent. No additional ethical approval was required for the current study because no new data were collected and all analyses were performed using previously collected data.

Participants aged 18–74 years who were free from stroke, myocardial infarction and cancer at baseline and for whom anthropometric (BMI, WC and WHtR) and organ-dysfunction data were available were included. The final numbers included in the prevalence estimates were 137,795 from the Kailuan Study, 436,203 from the UKB, 218,841 from the AoU and 51,269 from the SIDIAP. The progression from preclinical obesity to clinical obesity was estimated among those with CAD-confirmed obesity but without any organ dysfunction, and the sample size was 8,009, 29,338, 54,535 and 5,273, respectively. For the mortality analysis, the AoU study was excluded owing to its relatively short follow-up duration; for the other three cohorts, the sample size was generally the same as that in the prevalence analysis, except for the Kailuan Study, in which three participants without valid mortality data were further excluded. Details of the study design for each cohort can be found in the Supplementary Methods, and the selection of study participants is in Supplementary Figs. 1–4.

Definitions of clinical and preclinical obesity

Following criteria from the *Lancet* Commission[1], clinical obesity was defined as excess adiposity plus at least one sign of obesity-induced organ dysfunction. Preclinical obesity was defined as excess adiposity without such dysfunction.

Excess adiposity was defined by any of the following criteria, to be consistent with the proposed framework: (1) BMI ≥ 40 kg m^{-2}; (2) BMI ≥ 30 kg m^{-2} (≥28 for Chinese individuals) plus elevated WC or WHtR; or (3) BMI 25–30 kg m^{-2} (24–28 for Chinese individuals) plus both elevated WC and WHtR. The thresholds for population-specific WC-defined adiposity are ≥102 cm for male and ≥88 cm for female individuals in the Western population, and ≥90 cm for male and ≥85 cm for female individuals in the Chinese population[8,9]. The thresholds for race- and sex-specific WHtR-defined adiposity are 0.57 (male) and 0.58 (female) for non-Hispanic white individuals; 0.55 (male) and 0.57 (female) for non-Hispanic Black individuals; 0.57 (male) and 0.59 (female) for Hispanic individuals; 0.56 (male) and 0.59 (female) for Asian individuals; and 0.50 for others[10]. To illustrate that the commonly used WHtR cut-off of 0.50 (ref. 26) is not an appropriate measure for central obesity, the bivariate scatter plots between BMI and WHtR were generated with fitted linear regression lines. The optimal cut-off values for WHtR that correspond to established BMI thresholds of obesity (28 kg m^{-2} for Chinese individuals and 30 for others) were derived from the linear regression lines given the very high Pearson correlation coefficients in the four cohorts ($r \geq 0.64$).

Organ dysfunction was defined as the presence of at least one of 18 clinical indicators listed in the Commission report. Notably, in line with the Commission's recommendations, the metabolic cluster criterion for clinical obesity (hyperglycaemia together with low high-density lipoprotein (HDL) and high triglycerides) was considered to be met only when diabetes and dyslipidaemia occurred together, and not when either condition occurred alone. Data availability about organ dysfunction ranged from 9 (SIDIAP) to 18 (UKB) indicators. Case ascertainment was based on medical records, self-reports and health assessments (Supplementary Table 2).

Covariates

Socio-demographic and lifestyle data were collected for each cohort; details can be found in the Supplementary Methods.

Outcomes

Organ dysfunction and death events were identified through self-reports, clinical exams, medical records and provincial death certificates in the Kailuan Study. In the UKB, events were ascertained through linkages with hospital records and death registries. Incident organ dysfunctions were obtained through EHRs in the AoU study, with measurements recorded at different time points and clinic visits. Outcomes in the SIDIAP were identified through linkage to primary care and hospital EHRs.

Measures of prevalence and incidence

Given the challenges in establishing causality between obesity and coexisting organ dysfunction at the individual level, we applied the AF approach at the population level to quantify the proportion of organ dysfunction cases attributable to obesity among individuals with obesity[11]. The AF was calculated as: $\mathrm{AF} = \frac{\mathrm{HR}-1}{\mathrm{HR}}$, where HR denotes the hazard ratio for the association between obesity and risk of incident organ dysfunction with adjustment for relevant confounders using Cox proportional hazards models. Details are provided in the Supplementary Methods.

Statistical analysis

Descriptive statistics were reported as mean (s.d.), median (interquartile range) or percentages, as appropriate. Multiple imputations using chained equations (linear and logistic regression) were used to impute the missing data (mice package in R, v.3.19.0). Prevalence estimates and 95% CIs were calculated using the epi.conf function from the epiR package in R (v.2.0.95). To quantify the misclassification of obesity by BMI alone, we estimated the prevalence of abdominal obesity (based on WC and/or WHtR) in each BMI category. We further estimated the prevalence of clinical obesity among people with obesity, as well as among the total population, with adjustment using the AF method. The AF-adjusted prevalence of clinical obesity was estimated by multiplying the crude prevalence of clinical obesity and the corresponding AF values in each cohort. The unadjusted prevalence (that is, the observed prevalence) was considered as the maximum of the prevalence of clinical obesity.

Using longitudinal data from all four cohorts, we estimated the cumulative incidence of incident organ dysfunction among individuals with preclinical obesity. Follow-up time was calculated from baseline until the first occurrence of incident organ dysfunction, death or end of follow-up. Cumulative incidence curves were estimated using Kaplan–Meier methods implemented in the survival package in R (v.3.8.6), with cumulative incidence calculated as 1 minus the survival probability. The

AF-adjusted cumulative incidence of clinical obesity was estimated by multiplying the observed cumulative incidence of organ dysfunction by the corresponding AF estimates in each cohort.

For mortality risk analysis, participants were categorized into four groups: (1) no confirmed obesity and no organ dysfunction (reference group); (2) no confirmed obesity but with organ dysfunction; (3) confirmed obesity without organ dysfunction (preclinical obesity); or (4) confirmed obesity with organ dysfunction (clinical obesity). To evaluate whether the composite anthropometric criteria could detect high-risk individuals misclassified by BMI alone, we conducted the analysis of the association between obesity status and mortality in the following five groups: (1) no overweight or obesity (BMI < 24/25; reference group); (2) BMI-based overweight without CAD-obesity; (3) BMI-based overweight with CAD-obesity (that is, both elevated WC and elevated WHtR; this group can be viewed as the underdiagnosis of obesity by BMI alone); (4) BMI-based obesity without CAD-obesity (this group can be viewed as the overdiagnosis of obesity by BMI alone); and (5) BMI-based obesity with CAD-obesity. To further evaluate the effects of composite anthropometric criteria for excessive adiposity, participants were categorized into eight groups based on BMI-defined obesity status (yes, no), CAD-obesity status (yes, no) and presence of organ dysfunction (yes, no) at baseline.

The association between obesity subtypes and mortality was estimated using the Cox proportional hazards models implemented in the survival package in R (v.3.8-6). Study-specific HRs and 95% CIs were pooled using fixed-effects meta-analysis implemented in the meta package in R (v.8.5.0). Time-at-risk extended from baseline to death or administrative censoring (31 December 2023 for the Kailuan Study, 19 December 2022 for the UKB and 31 December 2021 for the SIDIAP). Proportional hazards assumptions were verified using log–log survival plots. We performed several robustness checks, such as excluding deaths occurring within the first 2 or 5 years after baseline or including waist-to-hip ratio (≥0.90 for male and ≥0.85 for female individuals) as an additional criterion for central obesity. Stratified analyses by age groups (<60 and ≥60 years old), sex (male and female) and smoking status (never, former and current) were further performed to test the robustness of the results across subgroups of the participants.

All analyses were performed using SAS v.9.4 and R v.4.4.2. Statistical significance was defined as $P < 0.05$ (two-sided).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The All of Us Research Program data used in this study are available through the All of Us Researcher Workbench (https://workbench.researchallofus.org) after registration and approval. The UK Biobank data used in this study are available through the UK Biobank Research Analysis Platform (https://www.ukbiobank.ac.uk) after registration and approval (application number 109546). The Kailuan Study data are not publicly available because of participant privacy restrictions. Deidentified data may be made available upon reasonable request to S.W. at drwusl@163.com, pending application and approval by the steering committee of the cohort. The SIDIAP data were sourced from EHRs and are only available for the participating researchers, in accordance with current European and national laws. Data may be shared on reasonable request to the participating researchers, with permission from SIDIAP's Scientific Committee and the Clinical Research Ethics Committee of IDIAP Jordi Gol, but are not publicly available for legal reasons related to data privacy protection.

Code availability

The code used in this study is available on Zenodo at https://doi.org/10.5281/zenodo.20256910 (ref. 27).

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Author contributions A.P., S.Y., R.R., X.L. and J.X. contributed equally to this work and share first authorship. A.P. led the statistical analysis plan, coordinated multi-cohort harmonization, oversaw analysis of the UKB study and contributed to writing of the manuscript, especially the Methods and results. S.Y. performed cohort-specific data extraction and quality control for the AoU study, managed literature synthesis and contributed to drafting the results and Supplementary Information. R.R. led cohort-specific data extraction and quality control for the SIDIAP database, contributed to literature synthesis and assisted in drafting the results and Supplementary Information. X.L. led the analysis of the UKB study, performed cohort-specific data extraction and contributed to drafting the results and Supplementary Information. J.X. led the analysis of the Kailuan Study, and contributed to writing the Methods and results. Co-senior authors F.R., J.M.F.-R., E.R. and S.W. jointly supervised the work and share senior authorship. F.R. conceived the study, led coordination across study sites, contributed to the interpretation of the results and provided major input in the draft of the manuscript and its revisions. J.M.F.-R. contributed to conceiving the study, oversaw analysis of the SIDIAP data, contributed to interpretation of the overall results, elaborated the first preliminary draft of the manuscript and supervised revisions. E.R. supervised methodological analysis of the AoU study and supervised revisions. S.W. oversaw analysis of the Kailuan Study, contributed to interpretation of the overall results and supervised revisions. R.H.E. and G.M. contributed to study design and discussion and interpretation of data and provided critical input for preparation of the manuscript and its revisions. H.L., T.G., J.J., S.C. and J.B. contributed to cohort-specific data extraction, harmonization and technical validation of EHR-derived variables. All authors reviewed and approved the final manuscript and take full responsibility for the integrity of the data and analysis.

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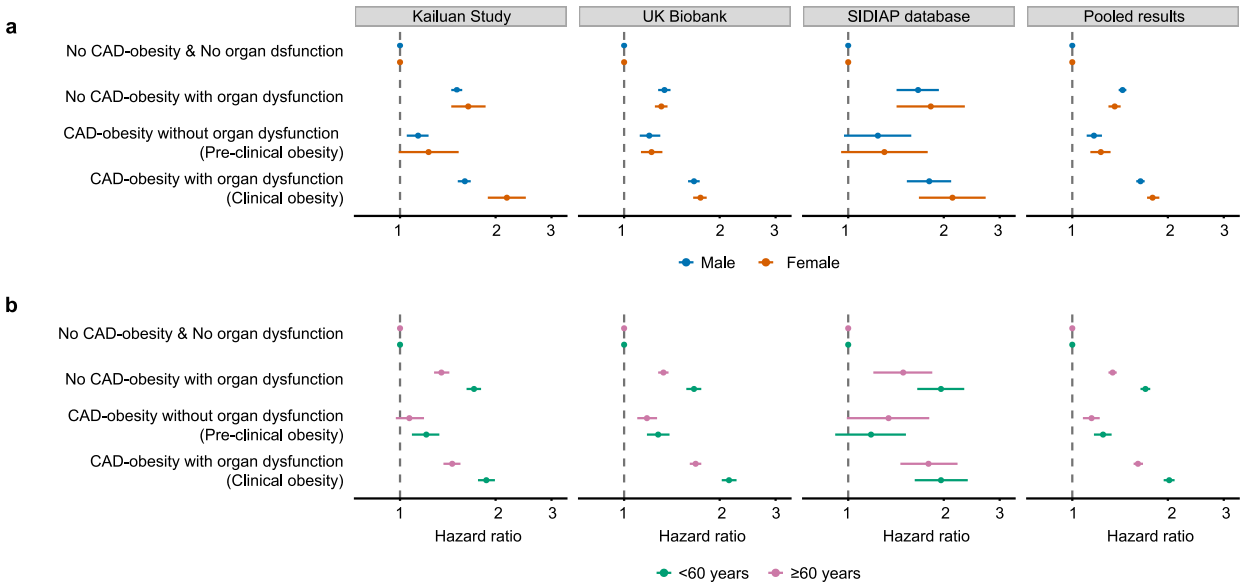
Competing interests A.P., S.Y., R.R., X.L., J.X., H.L., J.J., S.C., T.G., S.W., J.M.F.-R. and J.B. declare no competing interests. G.M. reports consulting fees from Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Medtronic, Fractyl and Recor. She is also a scientific advisor for Keyron, MetaDeq, GHP Scientific and Jemyll. R.H.E. reports receiving consulting fees from Novo Nordisk, the Healthy Aging Company and WW International. E.R. reports consulting fees from Energesis Pharmaceuticals, Eli Lilly, Merck, Amway, Novo Nordisk, Altimmune, AbbVie, Amgen, Orbimed and Boehringer Ingelheim. F.R. reports research grants from Ethicon (Johnson & Johnson), Novo Nordisk and Medtronic, consulting fees from Kailera and speaking honoraria from Medtronic, Ethicon, Novo Nordisk, Eli Lilly, Amgen, Regeneron and Astra Zeneca. F.R. is also a member of the data safety monitoring board for GI Metabolic Solutions and the president of the Metabolic Health Institute, a non-profit organization.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-026-11237-5.

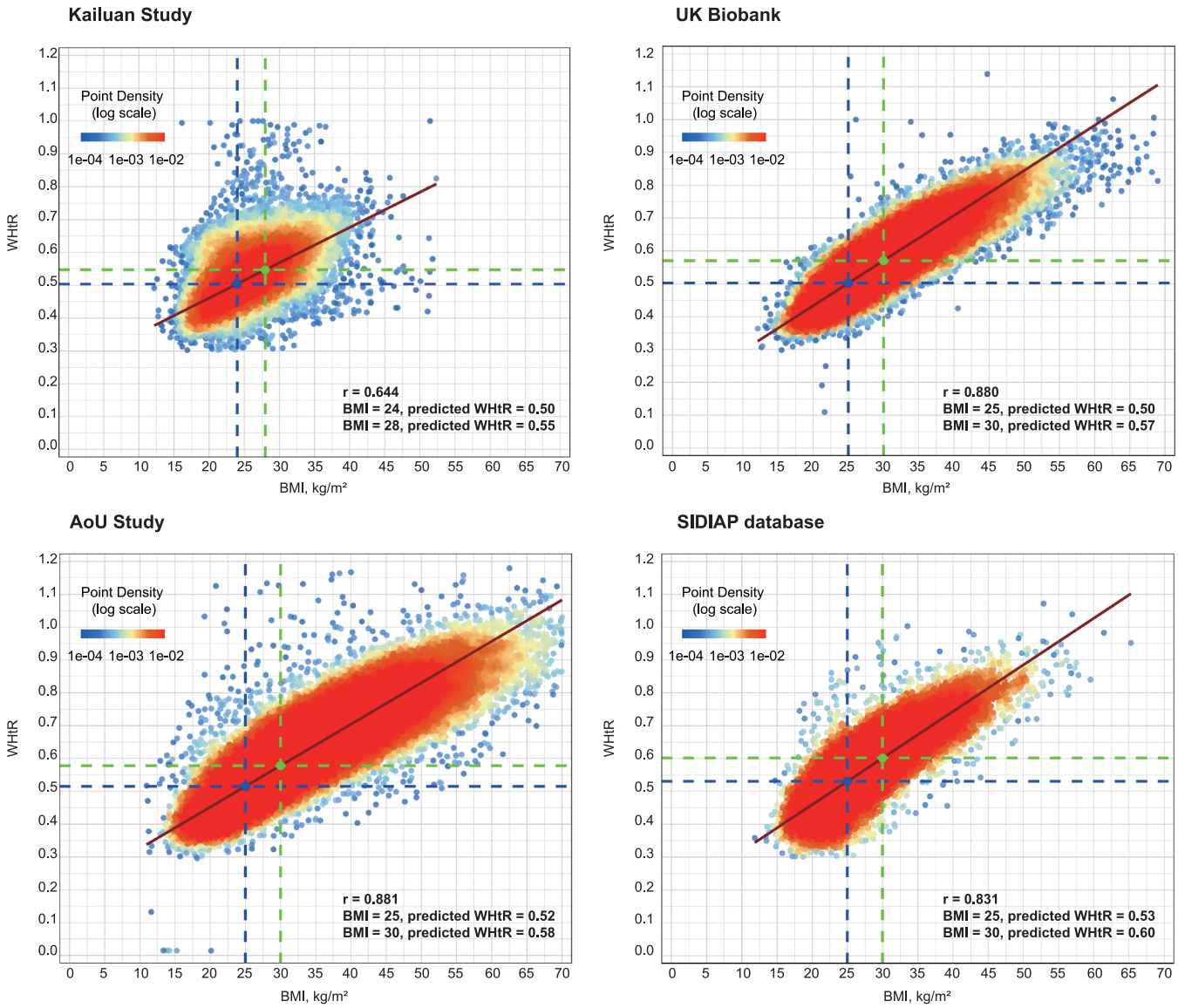
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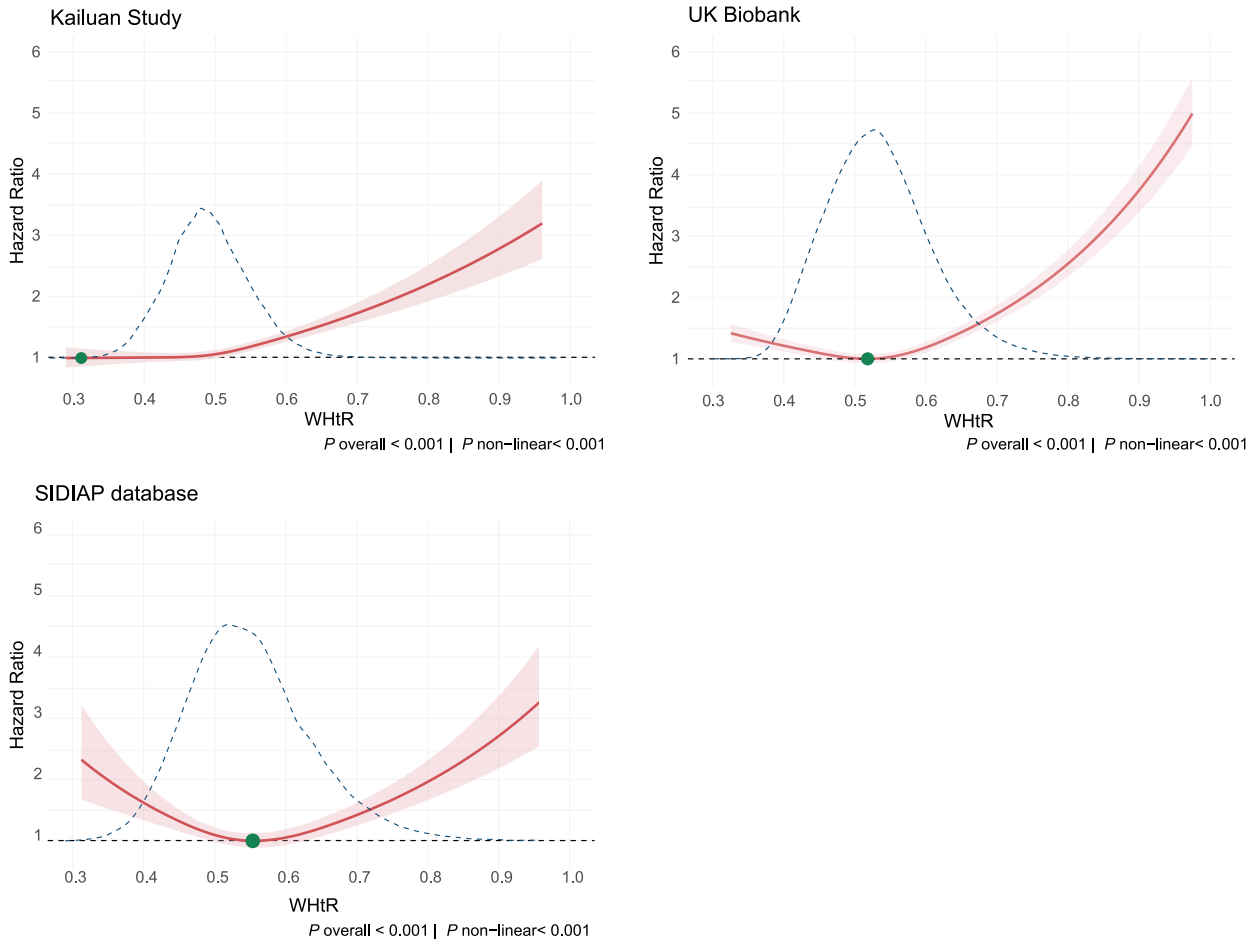
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Extended Data Fig. 1 | Subgroup analysis of the association between clinical obesity and risk of all-cause mortality. Results are shown as HRs and 95% CIs from the Cox proportional hazards model. The analyses included 137,792 participants with 17,642 deaths in the Kailuan Study, 436,203 participants with 31,812 deaths in the UK Biobank and 51,269 participants with 2,338 deaths in the SIDIAP database. Points indicate HR point estimates and horizontal lines indicate 95% CIs. Models were adjusted for demographic factors (age and sex in all studies and, in addition, ethnicity in the UK Biobank), socio-economic status (marital status, educational level and household income in the Kailuan Study; employment, education and Townsend deprivation index in the UK Biobank; and MEDEA deprivation index in the SIDIAP) and lifestyle factors (smoking and alcohol consumption in all studies; physical activity in the Kailuan Study; and physical activity, diet quality and sleep duration in the UK Biobank). Interactions of obesity status with sex and age group were evaluated using joint Wald tests of the corresponding interaction terms; all $P_{interaction}$ values were <0.001. Pooled estimates were obtained using a fixed-effect meta-analysis model. All statistical tests were two-sided. In panel **a**, blue and orange represent men and female, respectively. In panel **b**, green and purple represent participants aged <60 years and ≥60 years, respectively. **a**, Sex-stratified analyses. **b**, Age-stratified analyses.



Extended Data Fig. 2 | Associations between BMI and WHtR. Scatter plots showing the association between BMI and WHtR among 137,795 participants in the Kailuan Study, 436,203 participants in the UK Biobank, 218,841 participants in the All of Us Research Program and 51,269 participants in the SIDIAP database. Each point represents one participant. Points are coloured according to log-transformed point density. The solid line represents the fitted linear regression relationship between BMI and WHtR. Dashed vertical lines indicate BMI thresholds for overweight and obesity, defined as 24 and 28 kg/m^2 in the Kailuan Study and 25 and 30 kg/m^2 in the other cohorts. Dashed horizontal lines indicate the predicted WHtR values corresponding to these BMI thresholds based on the fitted linear regression models. Pearson correlation coefficients (r) between BMI and WHtR are shown within each panel. Pearson correlation tests were two-sided and statistically significant ($P < 0.001$). BMI was expressed as kg m^{-2}, and WHtR was calculated as WC divided by height.



Extended Data Fig. 3 | Associations between WHtR and all-cause mortality. Restricted cubic spline curves showing the associations between WHtR and all-cause mortality among 137,792 participants with 17,642 deaths in the Kailuan Study, 436,203 participants with 31,812 deaths in the UK Biobank and 51,269 participants with 2,338 deaths in the SIDIAP database. HRs and 95% CIs were estimated using Cox proportional hazards models adjusted for demographic factors, socio-economic status and lifestyle factors. The solid red lines indicate HRs, and the shaded areas indicate 95% CIs. The horizontal dashed line represents a HR of 1.0. Green dots indicate the reference values of WHtR in each cohort. Blue dashed curves indicate the density distribution of WHtR. Overall and nonlinear associations were assessed using two-sided Wald chi-square tests, with corresponding P values shown within each panel (Kailuan: $P_{overall} = 5.99 \times 10^{-29}$, $P_{nonlinear} = 5.01 \times 10^{-05}$; UK Biobank: $P_{overall} = 4.75 \times 10^{-253}$, $P_{nonlinear} = 2.58 \times 10^{-87}$; SIDIAP: $P_{overall} = 9.47 \times 10^{-20}$, $P_{nonlinear} = 2.90 \times 10^{-12}$).

Extended Data Table 1 | Prevalence of obesity defined by different anthropometric measures

	CAD-obesity	Obesity defined by BMI alone	Obesity defined by WC alone	Obesity defined by WHtR alone
Kailuan Study				
Overall	21.3 (21.1-21.5)	17.8 (17.6-18.0)	39.4 (39.1-39.6)	18.3 (18.0-18.5)
Female	17.1 (16.6-17.5)	15.8 (15.4-16.2)	37.1 (36.5-37.7)	12.6 (12.2-13.0)
Male	22.3 (22.1-22.6)	18.3 (17.6-18.9)	39.9 (39.6-40.2)	19.6 (19.4-19.8)
UK Biobank				
Overall	27.3 (27.1-27.4)	24.0 (23.9-24.1)	33.0 (32.9-33.1)	27.2 (27.1-27.3)
Female	25.5 (25.4-25.7)	23.4 (23.2-23.6)	35.9 (35.7-36.1)	21.4 (21.2-21.6)
Male	29.3 (29.1-29.5)	24.7 (24.5-24.9)	29.5 (29.3-29.7)	34.1 (33.9-34.3)
AoU Study				
Overall	48.1 (47.9-48.3)	42.5 (42.3-42.7)	53.1 (52.9-53.3)	48.8 (48.6-49.0)
Female	51.4 (51.2-51.7)	45.8 (45.6-46.1)	60.1 (59.9-60.4)	48.4 (48.1-48.7)
Male	42.8 (42.5-43.1)	37.2 (36.8-37.5)	41.7 (41.4-42.0)	49.5 (49.2-49.9)
SIDIAP database				
Overall	26.1 (25.7-26.5)	18.7 (18.4-19.1)	31.6 (31.2-32.0)	33.3 (32.9-33.7)
Female	29.1 (28.6-29.7)	17.9 (17.4-18.4)	42.8 (42.2-43.4)	31.2 (30.7-31.8)
Male	23.1 (22.5-23.6)	19.5 (19.1-20.0)	20.4 (19.9-20.9)	35.3 (34.7-35.9)

This table presents the prevalence estimates and 95% CIs of obesity defined by different anthropometric measures. The analyses included 137,795 participants from the Kailuan Study, 436,203 participants from the UK Biobank, 218,841 participants from the All of Us (AoU) Research Program and 51,269 participants from the SIDIAP database. Prevalence estimates are presented as percentages with 95% CIs. The combined anthropometric definition of obesity is described in detail in the Methods.

Extended Data Table 2 | Hazard ratios and attributable fractions of CAD-obesity associated with organ dysfunctions

	Overall		Female		Male	
	HR (95% CI)	AF	HR (95% CI)	AF	HR (95% CI)	AF
Kailuan Study	1.62 (1.58-1.66)	0.383	1.72 (1.63-1.82)	0.419	1.57 (1.53-1.61)	0.363
UK Biobank	1.68 (1.64-1.72)	0.405	1.81 (1.75-1.87)	0.448	1.53 (1.47-1.59)	0.346
AoU Study	1.67 (1.61-1.73)	0.401	1.70 (1.62-1.77)	0.412	1.57 (1.48-1.66)	0.363
SIDIAP database	2.07 (1.97-2.18)	0.517	2.06 (1.91-2.22)	0.515	2.08 (1.93-2.25)	0.519

The analyses included 70,081 participants in the Kailuan Study, 188,964 participants in the UK Biobank, 138,588 participants in the All of Us (AoU) Research Program and 32,954 participants in the SIDIAP database. HRs were estimated using Cox proportional hazards models adjusted for demographic factors (age and sex in all, and, in addition, race/ethnicity in the AoU study and ethnicity in the UK Biobank), socio-economic status (marital status, educational level and household income in the Kailuan Study, and, in addition, employment, education and Townsend deprivation index in the UK Biobank; educational level and household income in the AoU study; and MEDEA deprivation index in SIDIAP) and lifestyle factors (smoking and alcohol consumption in all studies, and, in addition, physical activity in the Kailuan Study and physical activity, diet quality and sleep duration in the UK Biobank). All statistical tests were two-sided. AF was calculated as follows: $AF=(HR-1)/HR$.

Extended Data Table 3 | Prevalence of preclinical obesity and clinical obesity before and after attributable adjustment

	Participants with CAD-obesity				Overall population			
	CAD-obesity with organ dysfunction	CAD-obesity without organ dysfunction	Clinical obesity (AF adjusted)	Pre-clinical obesity (AF adjusted)	CAD-obesity with organ dysfunction	CAD-obesity without organ dysfunction	Clinical obesity (AF adjusted)	Pre-clinical obesity (AF adjusted)
Kailuan Study								
Overall	68.6 (68.1-69.2)	31.4 (30.8-31.9)	26.3 (25.2-27.3)	73.7 (72.7-74.8)	14.6 (14.4-14.8)	6.68 (6.55-6.82)	5.60 (5.36-5.83)	15.7 (15.1-16.3)
Female	62.5 (61.1-64.0)	37.5 (36.0-38.9)	26.2 (24.2-28.2)	73.8 (71.8-75.8)	10.7 (10.3-11.0)	6.39 (6.10-6.69)	4.47 (4.09-4.84)	12.6 (11.6-13.6)
Male	69.8 (69.2-70.3)	30.2 (29.7-30.8)	25.3 (24.2-26.5)	74.7 (73.5-75.8)	15.6 (15.4-15.8)	6.75 (6.61-6.90)	5.66 (5.39-5.92)	16.7 (16.1-17.3)
UK Biobank								
Overall	75.3 (75.1-75.6)	24.7 (24.4-24.9)	30.5 (29.4-31.6)	69.5 (68.4-70.6)	20.5 (20.4-20.7)	6.73 (6.65-6.80)	8.32 (8.02-8.61)	18.9 (18.4-19.5)
Female	72.0 (71.6-72.3)	28.0 (27.7-28.4)	32.2 (30.9-33.5)	67.8 (66.5-69.1)	18.4 (18.2-18.5)	7.16 (7.06-7.26)	8.22 (7.88-8.57)	17.3 (16.7-17.9)
Male	78.8 (78.5-79.2)	21.2 (20.8-21.5)	27.3 (25.3-29.3)	72.7 (70.7-74.7)	23.1 (22.9-23.3)	6.21 (6.10-6.32)	8.01 (7.41-8.61)	21.3 (20.4-22.2)
AoU Study								
Overall	56.7 (56.4-57.0)	43.3 (43.0-43.6)	22.7 (21.5-24.0)	77.3 (76.0-78.5)	27.3 (27.1-27.5)	20.9 (20.7-21.0)	10.9 (10.4-11.5)	37.3 (36.3-38.1)
Female	54.8 (54.4-55.2)	45.2 (44.8-45.6)	22.6 (20.9-24.2)	77.4 (75.8-79.1)	28.2 (27.9-28.4)	23.3 (23.0-23.5)	11.6 (10.9-12.3)	39.9 (38.6-41.0)
Male	60.3 (59.8-60.8)	39.7 (39.2-40.2)	21.9 (19.7-24.1)	78.1 (75.9-80.3)	25.8 (25.5-26.1)	17.0 (16.7-17.2)	9.37 (8.41-10.3)	33.4 (31.9-34.9)
SIDIAP database								
Overall	60.6 (59.8-61.4)	39.4 (38.6-40.2)	31.3 (30.9-31.8)	68.7 (68.2-69.1)	15.8 (15.5-16.1)	10.3 (10.0-10.6)	8.20 (8.10-8.30)	17.9 (17.8-18.0)
Female	56.7 (55.6-57.8)	43.3 (42.2-44.4)	29.2 (28.6-29.8)	70.8 (70.2-71.4)	16.5 (16.1-17.0)	12.6 (12.2-13.0)	8.50 (8.30-8.70)	20.6 (20.5-20.8)
Male	65.5 (64.3-66.7)	34.5 (33.3-35.7)	34.0 (33.4-34.6)	66.0 (65.4-66.6)	15.1 (14.7-15.6)	7.90 (7.60-8.30)	7.80 (7.70-8.00)	15.2 (15.1-15.4)

The analyses included 137,795 participants from the Kailuan Study, 436,203 participants from the UK Biobank, 218,841 participants from the All of Us (AoU) Research Program and 51,269 participants from the SIDIAP database. For population-level estimation, the prevalence of CAD-obesity was partitioned into three mutually exclusive observed or model-estimated components according to the presence of organ dysfunction and its estimated attribution based on AF analysis: (1) CAD-obesity without organ dysfunction, defined as individuals with CAD-obesity who did not present with any predefined organ dysfunction; (2) CAD-obesity with non-attributable organ dysfunction, defined as the estimated non-attributable component among participants with CAD-obesity and organ dysfunction, derived by applying the AF at the population level; and (3) clinical obesity (AF-adjusted), defined as the estimated attributable component among participants with CAD-obesity and organ dysfunction, derived using the AF. Groups 1 and 2 together represent preclinical obesity, referring to individuals with CAD-obesity but without organ dysfunction considered attributable to obesity. AF was calculated as follows: $AF=(HR-1)/HR$; $P_{\text{clinical obesity}|\text{obesity}}=AF\times P_{\text{organ dysfunction}|\text{obesity}}$; $P_{\text{clinical obesity}|\text{overall}}=P_{\text{clinical obesity}|\text{obesity}}\times P_{\text{obesity}|\text{overall}}$.

Extended Data Table 4 | Hazard ratios (95% CIs) for associations between five groups combining BMI categories and CAD-obesity status with mortality

	No overweight/obesity	Overweight without CAD-obesity	BMI-defined obesity only	Overweight with CAD-obesity	BMI-defined obesity with CAD-obesity
Kailuan Study					
Cases/person-years	6763/834819	5353/705268	440/63810	2063/132676	3023/300560
Model 1	1.00 (Reference)	0.96 (0.92-0.99)	1.10 (1.00-1.21)	1.12 (1.06-1.17)	1.17 (1.12-1.23)
Model 2	1.00 (Reference)	0.93 (0.90-0.97)	1.06 (0.96-1.17)	1.08 (1.02-1.13)	1.11 (1.06-1.16)
UK Biobank					
Cases/person-years	8795/1980800	10455/2214930	435/115133	2670/300947	9457/1293696
Model 1	1.00 (Reference)	0.88 (0.86-0.91)	0.86 (0.78-0.95)	1.17 (1.12-1.23)	1.25 (1.21-1.29)
Model 2	1.00 (Reference)	0.86 (0.84-0.89)	0.82 (0.74-0.90)	1.07 (1.02-1.12)	1.07 (1.04-1.11)
SIDIAP database					
Cases/person-years	698/252535	527/139815	13/6319	400/46660	700/94458
Model 1	1.00 (Reference)	0.75 (0.67-0.84)	0.69 (0.40-1.19)	1.01 (0.89-1.14)	1.09 (0.98-1.22)
Model 2	1.00 (Reference)	0.71 (0.63-0.80)	0.69 (0.40-1.19)	0.89 (0.78-1.01)	0.91 (0.81-1.01)
Pooled results					
Cases/person-years	16256/3068154	16335/3060013	888/185262	5133/480283	13180/1688714
Model 1	1.00 (Reference)	0.90 (0.88-0.92)	0.97 (0.91-1.04)	1.14 (1.10-1.17)	1.22 (1.19-1.25)
Model 2	1.00 (Reference)	0.88 (0.86-0.90)	0.93 (0.86-0.99)	1.06 (1.03-1.10)	1.07 (1.05-1.10)

The results are shown as HRs and 95% CIs from Cox proportional hazards models. The analyses included 137,792 participants in the Kailuan Study, 436,203 participants in the UK Biobank and 51,269 participants in the SIDIAP database. Model 1 was adjusted for demographic factors (age and sex in all studies and, in addition, ethnicity in the UK Biobank), socio-economic status (marital status, educational level and household income in the Kailuan Study; employment, education and Townsend deprivation index in the UK Biobank; and MEDEA deprivation index in the SIDIAP) and lifestyle factors (smoking and alcohol consumption in all cohorts; physical activity in the Kailuan Study; and physical activity, diet quality and sleep duration in the UK Biobank); model 2 was also adjusted for organ dysfunctions. Pooled estimates were obtained using a fixed-effect meta-analysis model. All statistical tests were two-sided.

The 'no overweight/obesity' group was defined as BMI < 24 kg m^{-2} in the Kailuan Study and <25 kg m^{-2} in the other studies. The 'overweight without CAD-obesity' group was defined as BMI in the overweight range but without both elevated WC and WHtR. The 'BMI-defined obesity only' group was defined as having obesity by BMI but neither elevated WC nor elevated WHtR, and this group could be viewed as those who were over-diagnosed as obese by BMI alone. The 'overweight with CAD-obesity' group was defined as having overweight by BMI plus having elevated WC and WHtR; this group could be viewed as those who were under-diagnosed as obese by BMI alone. The 'BMI-defined obesity with CAD-obesity' group was defined as having obesity by BMI plus having elevated WC or WHtR. The cut-off points for the elevated WC and WHtR are described in detail in the Methods.

Extended Data Table 5 | Hazard ratios (95% CIs) for association between clinical obesity and all-cause mortality

	No CAD-obesity & no organ dysfunction	No CAD-obesity but with organ dysfunction	Pre-clinical obesity (CAD-obesity & no organ dysfunction)	Clinical obesity (CAD-obesity with organ dysfunction)
Kailuan Study				
Cases/person-years	4083/903521	8473/700377	927/137808	4159/295428
Model 1	1.00 (Reference)	1.52 (1.46-1.58)	1.15 (1.07-1.24)	1.64 (1.57-1.71)
Model 2	1.00 (Reference)	1.53 (1.47-1.58)	1.15 (1.07-1.23)	1.65 (1.58-1.73)
UK Biobank				
Cases/person-years	6356/2196060	13329/2114803	1690/403462	10437/1191180
Model 1	1.00 (Reference)	1.39 (1.35-1.43)	1.34 (1.27-1.41)	1.96 (1.90-2.02)
Model 2	1.00 (Reference)	1.33 (1.29-1.37)	1.21 (1.15-1.28)	1.69 (1.63-1.74)
SIDIAP database				
Cases/person-years	383/291162	855/107507	148/55665	952/85453
Model 1	1.00 (Reference)	1.71 (1.50-1.95)	1.18 (0.97-1.43)	1.93 (1.69-2.20)
Model 2	1.00 (Reference)	1.71 (1.50-1.95)	1.24 (1.02-1.50)	1.93 (1.69-2.21)
Pooled results				
Model 1	1.00 (Reference)	1.44 (1.41-1.47)	1.27 (1.22-1.32)	1.85 (1.80-1.89)
Model 2	1.00 (Reference)	1.42 (1.39-1.45)	1.19 (1.14-1.24)	1.69 (1.64-1.73)

The results are shown as HRs and 95% CIs from Cox proportional hazards models. The analyses included 137,792 participants in the Kailuan Study, 436,203 participants in the UK Biobank and 51,269 participants in the SIDIAP database. Model 1 was adjusted for demographic factors (age and sex in all studies and, in addition, ethnicity in the UK Biobank); model 2 was also adjusted for socio-economic status (marital status, educational level and household income in the Kailuan Study; employment, education and Townsend deprivation index in the UK Biobank; and MEDEA deprivation index in the SIDIAP) and lifestyle factors (smoking and alcohol consumption in all cohorts; physical activity in the Kailuan Study; and physical activity, diet quality and sleep duration in the UK Biobank). Pooled estimates were derived using a fixed-effects model. All statistical tests were two-sided.

Extended Data Table 6 | Sensitivity analyses of the association between clinical obesity and all-cause mortality

	No CAD-obesity		Pre-clinical obesity	Clinical obesity
	No organ dysfunction	With organ dysfunction	CAD-obesity & no organ dysfunction	CAD-obesity with organ dysfunction
Exclusion of participants died within two years				
Kailuan Study (16,977 Cases, N=137,127)				
Cases/person-years	3908/903333	8148/700019	896/137776	4025/295276
Hazard ratio (95%CI)	1.00 (Reference)	1.53 (1.48-1.59)	1.16 (1.08-1.24)	1.67 (1.60-1.75)
UK Biobank (30,448 Cases, N=434,839)				
Cases/person-years	6106/2195756	12702/2114071	1619/403382	10021/1190697
Hazard ratio (95%CI)	1.00 (Reference)	1.31 (1.27-1.36)	1.21 (1.14-1.28)	1.69 (1.64-1.75)
SIDIAP (2,143 Cases, N= 51,074)				
Cases/person-years	343/291131	799/107464	139/55658	862/85384
Hazard ratio (95%CI)	1.00 (Reference)	1.74 (1.51, 1.99)	1.36 (1.12, 1.66)	1.93 (1.68, 2.22)
Pooled results				
Hazard ratio (95%CI)	1.00 (Reference)	1.42 (1.39-1.45)	1.20 (1.15-1.25)	1.69 (1.65-1.74)
Exclusion of participants died within five years				
Kailuan Cohort (14,870 Cases, N=135,020)				
Cases/person-years	3389/901451	7127/696278	803/137434	3551/293525
Hazard ratio (95%CI)	1.00 (Reference)	1.55 (1.49-1.62)	1.19 (1.10-1.29)	1.71 (1.63-1.79)
UK Biobank (26,467 Cases, N=430,858)				
Cases/person-years	5266/2192743	11032/2108054	1404/402609	8765/1186179
Hazard ratio (95%CI)	1.00 (Reference)	1.32 (1.28-1.37)	1.21 (1.14-1.29)	1.72 (1.66-1.78)
SIDIAP database (1,744 Cases, N=50,675)				
Cases/person-years	278/290821	632/106783	118/55568	716/84687
Hazard ratio (95%CI)	1.00 (Reference)	1.68 (1.44-1.96)	1.42 (1.14-1.77)	1.94 (1.66-2.27)
Pooled results				
Hazard ratio (95%CI)	1.00 (Reference)	1.41 (1.38–1.45)	1.21 (1.16–1.27)	1.72 (1.68–1.77)
Incorporate WHR into the diagnostic indicators for CAD-obesity[a]				
Kailuan Study (17,642 Cases, N=137,792)				
Cases/person-years	4083/903521	8473/700377	927/137808	4159/295428
Hazard ratio (95%CI)	1.00 (Reference)	1.52 (1.46-1.58)	1.09 (1.02 1.16)	1.62 (1.55-1.69)
UK Biobank (31,812 Cases, N=436,203)				
Cases/person-years	5765/2051406	11262/1839567	2281/548117	12504/1466416
Hazard ratio (95%CI)	1.00 (Reference)	1.33 (1.29-1.38)	1.19 (1.14-1.25)	1.64 (1.59-1.70)
Pooled results				
Hazard ratio (95%CI)	1.00 (Reference)	1.41 (1.37-1.44)	1.16 (1.11-1.20)	1.63 (1.59-1.68)

[a]Waist-to-hip ratio (WHR) cut-offs were defined as ≥0.90 for male and ≥0.85 for female.

The results are shown as HRs and 95% CIs from Cox proportional hazards models. Models were adjusted for demographic factors (age and sex in all studies and, in addition, ethnicity in the UK Biobank), socio-economic status (marital status, educational level and household income in the Kailuan Study; employment, education and Townsend deprivation index in the UK Biobank; and MEDEA deprivation index in the SIDIAP) and lifestyle factors (smoking and alcohol consumption in all studies; physical activity in the UK Biobank and the Kailuan Study; and diet quality and sleep duration in the UK Biobank). Pooled estimates were obtained using a fixed-effect meta-analysis model. All statistical tests were two-sided.

Extended Data Table 7 | Hazard ratios (95% CIs) for associations between eight groups combining BMI categories, CAD-obesity status and organ dysfunction status with mortality

	No CAD-obesity & no organ dysfunction		No CAD-obesity but with organ dysfunction		Pre-clinical obesity		Clinical obesity	
	BMI- & Confirmed- & Dysfunction-	BMI+ & Confirmed- & Dysfunction-	BMI- & Confirmed- & Dysfunction+	BMI+ & Confirmed- & Dysfunction+	BMI- & Confirmed+ & Dysfunction-	BMI+ & Confirmed+ & Dysfunction-	BMI- & Confirmed+ & Dysfunction+	BMI+ & Confirmed+ & Dysfunction+
Kailuan Study								
N, %	59212 (42.97%)	1659 (1.2%)	44952 (32.62%)	2607 (1.89%)	3231 (2.34%)	5977 (4.34%)	5869 (4.26%)	14285 (10.37%)
Cases/person-years	3983/878992	100/24529	8133/661096	340/39281	482/48596	445/89212	1581/84080	2578/211348
Model 1	1.00 (Reference)	1.20 (0.98-1.46)	1.52 (1.46-1.58)	1.55 (1.39-1.74)	1.19 (1.08-1.30)	1.13 (1.02-1.24)	1.64 (1.54-1.74)	1.65 (1.57-1.74)
Model 2	1.00 (Reference)	1.18 (0.97-1.44)	1.53 (1.47-1.59)	1.55 (1.39-1.73)	1.17 (1.06-1.28)	1.14 (1.03-1.25)	1.64 (1.55-1.74)	1.67 (1.59-1.75)
UK Biobank								
N, %	156371 (35.85%)	3255 (0.75%)	152431 (34.94%)	5171 (1.19%)	6147 (1.41%)	23191 (5.32%)	16488 (3.78%)	73149 (16.77%)
Cases/person-years	6236/2151022	120/45039	13014/2044708	315/70095	447/83728	1243/319734	2223/217219	8214/973961
Model 1	1.00 (Reference)	1.08 (0.91-1.30)	1.39 (1.35-1.44)	1.22 (1.09-1.36)	1.30 (1.18-1.43)	1.35 (1.27-1.44)	1.86 (1.77-1.95)	1.99 (1.93-2.06)
Model 2	1.00 (Reference)	1.03 (0.86-1.23)	1.33 (1.29-1.37)	1.14 (1.02-1.28)	1.19 (1.08-1.31)	1.22 (1.14-1.29)	1.63 (1.56-1.72)	1.70 (1.65-1.76)
SIDIAP database								
N, %	27235 (53.1%)	446 (0.9%)	10038 (19.6%)	171 (0.3%)	1684 (3.3%)	3589 (7.0%)	2712 (5.3%)	5394 (10.5%)
Cases/person-years	382/286602	1/4560	843/105747	12/1760	55/17881	93/37785	345/28780	607/56674
Model 1	1.00 (Reference)	-	1.68 (1.48-1.92)	1.87 (1.05-3.34)	1.05 (0.79-1.40)	1.25 (0.99-1.56)	1.86 (1.58-2.18)	1.93 (1.68-2.22)
Model 2	1.00 (Reference)	-	1.70 (1.49-1.94)	1.63 (0.91-2.89)	1.10 (0.83-1.47)	1.32 (1.05-1.65)	1.87 (1.59-2.19)	1.93 (1.68-2.23)
Pooled results								
Cases/person-years	10601/3316616	221/74128	21990/2811551	667/111136	984/150205	1781/446731	4149/330079	11399/1241983
Model 1	1.00 (Reference)	1.13 (0.99-1.29)	1.45 (1.41-1.48)	1.38 (1.28-1.49)	1.23 (1.15-1.31)	1.28 (1.22-1.35)	1.78 (1.71-1.84)	1.89 (1.84-1.94)
Model 2	1.00 (Reference)	1.10 (0.96-1.25)	1.41 (1.38-1.44)	1.34 (1.24-1.45)	1.18 (1.10-1.26)	1.20 (1.14-1.26)	1.65 (1.59-1.71)	1.70 (1.65-1.74)

The results are shown as HRs and 95% CIs from Cox proportional hazards models. The definitions of BMI categories, CAD-obesity and organ dysfunction status are described in the Methods. Model 1 was adjusted for demographic factors (age and sex in all studies and, in addition, ethnicity in the UK Biobank); model 2 was also adjusted for socio-economic status (marital status, educational level and household income in the Kailuan Study; employment, education and Townsend deprivation index in the UK Biobank; and MEDEA deprivation index in the SIDIAP) and lifestyle factors (smoking and alcohol consumption in all cohorts; physical activity in the Kailuan Study; and physical activity, diet quality and sleep duration in the UK Biobank). Pooled estimates were derived using a fixed-effects model. All statistical tests were two-sided.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection
Data analysis	All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). R packages used for statistical analyses and visualization included mice (version 3.19.0) epiR (version 2.0.95), survival (version 3.8.6), meta (version 8.5.0), ggplot2 (version 4.0.3), and rms (version 8.1.1). No new statistical algorithms or software packages were developed. Custom analysis scripts are available at Zenodo (https://doi.org/10.5281/zenodo.20256910).

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Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The All of US data and UK Biobank data (application number 109546) are publicly available and can be accessed by registration at https://

workbench.researchallofus.org and https://www.ukbiobank.ac.uk/. The Kailuan data described in the manuscript can be made available upon reasonable request to Prof Shouling Wu at drwusl@163.com, pending application and approval by the steering committee of the cohort. The SIDIAP data were sourced from Electronic Health Records and are only available for the participating researchers, in accordance with current European and national laws. Data could be shared on reasonable request to the participating researchers with permission of SIDIAP's Scientific Committee and Clinical Research Ethics Committee of IDIAPJ GoI, but not publicly available due to legal reasons related to data privacy protection.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was included as a biological variable in all cohorts and analyses. Sex information was obtained through self-report, medical records, or registry data depending on the cohort. Participants were categorized as male or female. Both sexes were included in the study, and sex was adjusted for in multivariable analyses where appropriate. Sex-stratified analysis was also conducted
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity data were available in the UK Biobank and All of Us cohorts, primarily through self-report. Ethnicity categories included White/non-White classifications in UK Biobank and non-Hispanic White, non-Hispanic Black, Hispanic, Asian, and Other categories in the All of Us Research Program. Socioeconomic variables, including education, income, deprivation indices, employment status, and lifestyle factors, were also collected across cohorts and incorporated into analyses where appropriate.
Population characteristics	The study included four large population-based cohorts: the Kailuan Study (n = 137,795; mean age 47.9 years; 80.6% male), UK Biobank (n = 436,203; mean age 56.0 years; 45.7% male), All of Us Research Program (n = 218,841; mean age 50.1 years; 38.2% male), and SIDIAP database (n = 51,269; mean age 43.4 years; 49.9% male). Across cohorts, the prevalence of current smoking ranged from 10.4% to 36.4%. The prevalence of obesity varied substantially according to different anthropometric criteria. Overall, waist circumference-defined obesity was the most prevalent anthropometric measure of excess adiposity, except in the SIDIAP database. Across cohorts, the prevalence of obesity defined by BMI, waist circumference, or waist-to-height ratio was generally highest in the All of Us Research Program and lowest in the Kailuan Study.
Recruitment	Participants were recruited through population-based cohort studies, healthcare systems, and electronic health record databases in China, the United Kingdom, the United States, and Spain. Recruitment procedures included standardized health assessments, questionnaires, physical examinations, biospecimen collection, and linkage to electronic health records where available. Potential sources of bias include volunteer participation bias, selection bias, and incomplete ascertainment of adiposity measures in routinely collected healthcare data.
Ethics oversight	The Kailuan Study was approved by the Ethics Committee of the Kailuan Medical Group. UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (application number 109546). The All of Us Research Program is overseen by the All of Us Institutional Review Board. The SIDIAP analysis was approved by the IDIAP Jordi GoI ethics committee (application number 20/204-P). All participants provided written informed consent where applicable. No additional ethical approval was required for the current study because no new data were collected and all analyses were conducted using previously collected data.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to predetermine sample size. Sample sizes were determined by the availability of eligible participants from four large population-based cohorts and electronic health record databases. The large sample size and substantial number of outcome events provided sufficient statistical power for the analyses performed.
Data exclusions	Participants with missing data on key exposure variables, or outcome variables were excluded according to pre-specified criteria described in the Methods section. Additional cohort-specific exclusion criteria can be seen in the flowchart.
Replication	No experimental replication was performed because of the observational study design. Instead, findings were evaluated across multiple independent population-based cohorts from different countries and healthcare settings to assess reproducibility and generalizability. Consistency of associations across cohorts supported the robustness of the findings.
Randomization	This was an observational study and participants were not randomized. Statistical models were adjusted for demographic, socioeconomic, lifestyle, and clinical covariates where appropriate.

Blinding	Blinding was not relevant to this observational cohort study because exposures and outcomes were derived from questionnaires, clinical assessments, and electronic health records using predefined criteria.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a