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Association of EASO-based obesity level with sleep patterns and the risk of all-cause and cardiovascular mortality

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Abstract

Background/Objectives

The EASO framework provides a clinical staging system for obesity, but its prognostic utility relative to BMI and interaction with sleep patterns regarding mortality remain understudied. This study evaluated the independent and joint associations of EASO- and BMI-defined obesity and sleep patterns with cardiovascular and all-cause mortality, and quantified the mediating role of sleep.

Subjects/Methods

This prospective cohort study included 408 453 UK Biobank adults. Obesity was classified using EASO stages and BMI categories. Sleep patterns were assessed via a composite score from five self-reported dimensions. Multivariable Cox models estimated hazard ratios, and mediation analysis quantified sleep's mediating role.

Results

During a median follow-up of 13.02 years, 34 146 all-cause and 6 991 cardiovascular deaths occurred. Both EASO- and BMI-defined obesity were independently associated with higher mortality risks. BMI-defined obesity yielded slightly larger relative risks. Participants with both obesity and adverse sleep patterns exhibited the highest mortality risk. Sleep patterns mediated 6.9% (95% CI, 3.7%–12.4%: $p < 0.001$) and 15.9% (95% CI, 9.2%–26.1%: $p < 0.001$) of the obesity–cardiovascular and obesity–all-cause mortality associations, respectively.

Conclusions

The EASO framework complements BMI in stratifying mortality risk. Sleep patterns partially mediate the obesity–mortality association, supporting sleep assessment and interventions in obesity risk-stratification strategies.

Introduction

Reducing premature all-cause mortality, of which cardiovascular disease (CVD) is the leading cause, remains a paramount global public health challenge (1, 2). This necessitates a deeper understanding of the interplay between modifiable risk factors. Among these, the concurrent epidemics of obesity and adverse sleep patterns stand out, not only due to their high prevalence but also because of their complex, potentially synergistic relationship (3–5). Understanding their combined impact on long-term health outcomes is critical for developing effective, integrated prevention strategies, yet this area remains underexplored.

Obesity, affecting over 600 million adults globally, is a well-established risk factor for mortality (3, 4). However, its conventional assessment using body mass index (BMI) has significant limitations, most notably its inability to account for abdominal adiposity—a more potent predictor of cardiometabolic risk (4, 5). To address this, the European Association for the Study of Obesity (EASO) has proposed a refined framework that incorporates waist-to-height ratio (WHtR) and comorbidity status, offering a more nuanced risk stratification (6, 7). Despite its theoretical advantages, the prognostic utility of the EASO framework for all-cause and CVD mortality has not been sufficiently validated in large-scale prospective cohorts, leaving a critical gap in clinical risk assessment.

Parallel to the obesity crisis, poor sleep health, encompassing abnormal duration, insomnia, and other disturbances, has become endemic, affecting up to 30% of adults in high-income nations (8, 9). While a"U-shaped" association between sleep duration and mortality is well-documented (10, 11), most research has relied on single-dimensional metrics. This oversimplification overlooks the multifaceted nature of sleep, including chronotype, snoring, and daytime sleepiness, which collectively constitute an individual's overall sleep pattern (12). Consequently, the true mortality risk attributable to comprehensive, multidimensionally-defined adverse sleep patterns may be substantially underestimated.

Crucially, obesity and poor sleep are not independent phenomena. A compelling body of evidence suggests a bidirectional relationship, wherein obesity can disrupt sleep architecture, while inadequate sleep can promote weight gain via neuroendocrine and behavioral pathways (9, 13). They also share common pathophysiological mechanisms, such as sympathetic nervous system activation, and metabolic dysregulation, which suggests the potential for synergistic effects on mortality risk (13). Examining these factors in isolation may therefore fail to capture their true public health impact.

To address these interconnected research gaps, we conducted a large-scale prospective analysis using the UK Biobank cohort (14, 15). Our study had two primary aims. First, to evaluate the association of obesity level based on the EASO framework, and a multidimensional sleep pattern with all-cause and CVD mortality. Second, to elucidate the joint effects of obesity and adverse sleep patterns on these outcomes. Through this comprehensive investigation, we aim to provide robust evidence to refine clinical risk stratification for obesity and to inform public health strategies that integrate sleep health management.

Methods

Study Design and Participants

This analysis was based on the UK Biobank resource, a large-scale prospective observational study of approximately 500 000 UK residents aged 40–69 years at recruitment (14, 15). At enrollment, extensive baseline data were collected, including self-reported information on lifestyle and health via touchscreen questionnaires, physical measurements performed by trained staff, and biological samples. The study was approved by the North West Multi-centre Research Ethics Committee, with all participants providing informed written consent.

Initially, the cohort comprised 502 401 participants from the UK Biobank. We excluded 1 297 individuals who had revoked consent. Additionally, 5 673 participants were excluded due to incomplete data on key covariates, including sociodemographic factors, smoking status, and alcohol consumption. Furthermore, 83 324 participants were excluded because their sleep patterns could not be ascertained. Consequently, the primary cohort for the all-cause mortality analysis consisted of 412 107 participants. We further excluded individuals with missing causes of death at baseline (n = 3 654), resulting in an analytical sample of 408 453 participants (**Supplementary Figure S1**).

Definition of Obesity level based on the EASO framework

In this study, participants were classified into five mutually exclusive weight categories based on the EASO framework, which integrates BMI, waist-to-height ratio (WHtR), and comorbidity status. Participants with a BMI of 18.5 to < 25.0 kg/m² were first divided into two groups: normal weight without morbidity (the reference category) and normal weight with morbidity, based on the absence or presence of comorbidities. A key feature of our approach was the stratification of individuals with a BMI from 25.0 to < 30.0 kg/m². Those within this range who had both a normal waist-to-height ratio (WHtR < 0.5) and no specified comorbidities were classified as Overweight (EASO overweight). Conversely, individuals in the same BMI range but with either an elevated WHtR (≥ 0.5) or at least one comorbidity were categorized as a distinct

high-risk group termed Obese, reclassified by EASO (EASO new obesity). The final obesity category, Obese, by BMI, comprised all individuals with a BMI of 30.0 kg/m² or greater, irrespective of other factors. Participants with a BMI < 18.5 kg/m² (Underweight) were excluded from the primary analyses due to their distinct pathophysiology.

The comorbidity status is consolidated from the diagnostic criteria of seven chronic conditions. The definitions for Hypertension (ICD-10: I10-I15, O10), cardiovascular disease (a composite endpoint including coronary heart disease (ICD-10: I21-I25), angina (I20), heart failure (I50), and stroke (I60-I64)), Diabetes (E10-E14, etc.), and chronic kidney disease (N18) integrate self-reported history, ICD-10 codes, clinical measurements, and medication use. Additionally, arthritis is defined based on ICD-10 codes (M05, M06, J99.0), COPD (chronic obstructive pulmonary disease) is based on ICD-10 codes (J40-J44), and depression combines ICD-10 codes (F32, F33) with questionnaire data (the International Classification of Diseases, 10th Revision (ICD-10)). The ascertainment of comorbidity status, a composite of seven chronic conditions, is detailed in **Supplementary Table S1**.

Assessment of sleep behaviors

Sleep behaviors were assessed using five self-reported items from the baseline questionnaire (**Supplementary Table S2**). These included: chronotype (morning vs. evening preference), sleep duration (< 7, 7–8, or ≥ 9 hours/day), insomnia symptoms (frequency of trouble sleeping), snoring (yes/no), and daytime sleepiness (likelihood of dozing off). Following established methods (16), For each behavior, participants were assigned a score of 0 for a low-risk profile or 1 for a high-risk profile. The low-risk categories were defined as: an early chronotype (morning preference), a sleep duration of 7–8 hours per day, never/rarely experiencing insomnia, no self-reported snoring, and infrequent daytime sleepiness. The individual scores were summed to create an overall sleep score ranging from 0 (all low-risk) to 5 (all high-risk). Based on this score, participants were categorized into three sleep patterns: healthy (score of 0), intermediate (score of 1–2), and poor (score of 3–5) (16–18).

Ascertainment of outcomes

Participants were followed from the baseline assessment until death, loss to follow-up, or the end of the follow-up period (30 September 2021 for England and Wales; 31 October 2021 for Scotland). The primary outcomes were all-cause mortality and cardiovascular mortality. Mortality data were ascertained through linkage to national death registries (NHS Digital and National Records of Scotland). Cardiovascular mortality was defined using ICD-10 codes I00-I99 as the primary cause of death (**Supplementary Table S3)**.

Covariates

Covariates were selected based on prior literature and clinical relevance. Sociodemographic characteristics included age at baseline (as a continuous variable), sex (male or female), and self-reported ethnicity (categorized as White, Asian, Black, or Other). Socioeconomic status was quantified using the Townsend Deprivation Index (TDI), an area-based composite measure of material deprivation, which was treated continuously. Lifestyle factors comprised smoking status (classified as never, former, or current) and binge drinking. Binge drinking was defined as a binary variable indicating the consumption of eight or more standard units of alcohol for men, or six or more for women, on a single occasion (14, 15).

Statistical analyses

Baseline characteristics of the study population were summarized according to obesity categories (defined by the EASO framework). Differences across these groups were evaluated using chi-square tests for categorical variables and one-

way analysis of variance (ANOVA) for continuous variables.

We employed Cox proportional hazards regression models to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the associations of obesity status with all-cause and cardiovascular mortality (19, 20). Three sequentially adjusted models were constructed: a minimally adjusted model for age and sex (Model 0); a multivariable model further adjusted for ethnicity, Townsend deprivation index, binge drinking, and smoking status (Model 1); and a final model that additionally included sleep patterns (Model 2) to assess their independent contribution (19, 20). Furthermore, to quantify the public health burden, population attributable fractions (PAFs) were calculated to estimate the proportion of mortality cases that could potentially be prevented if all individuals with excess weight or morbidity achieved normal weight without morbidity (21). This was calculated using proportional hazards models with a piecewise constant baseline hazard function.

To explore the joint association of obesity status and sleep patterns with mortality, a composite variable with 15 categories was created by combining the five obesity statuses and three sleep patterns. The group with normal weight without morbidity and a healthy sleep pattern served as the reference. We assessed for interaction on both additive and multiplicative scales. Additive interaction was evaluated by calculating the relative excess risk due to interaction (RERI), while multiplicative interaction was tested using the likelihood ratio test by comparing models with and without the product term.

To elucidate potential pathways, we conducted a mediation analysis to assess the extent to which obesity level mediated the association between sleep patterns and mortality outcomes. The proportion mediated was estimated using the difference in coefficients method (22). Finally, a series of analyses were performed to assess the robustness of our findings. We conducted stratified analyses to explore potential effect modification by age (< 65 vs. ≥ 65 years), sex (male vs. female), and ethnicity (White vs. non-White). In a key sensitivity analysis, we excluded participants who experienced an event within the first year of follow-up to mitigate potential reverse causation. All statistical analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Cohort

The study cohort included 408 453 participants with a mean age of 56.49 (SD 8.07) years; 224 220 (54.9%) were male. Baseline characteristics are detailed in Table 1. Participants were categorized into five groups based on the EASO framework: normal weight without morbidity (n = 56 852), normal weight with morbidity (n = 77 930), EASO overweight (n = 157 334), EASO new obesity (n = 17 506), and BMI obesity (n = 98 831). Compared with individuals in the normal weight without morbidity group, those in progressively higher obesity categories were generally older, experienced greater socioeconomic deprivation, and had higher rates of smoking. As expected, the WHtR increased steadily with each category. Furthermore, a clear gradient was observed for sleep-related factors: increasing obesity was associated with shorter sleep duration, a greater prevalence of evening chronotype, and higher frequencies of insomnia, snoring, daytime dozing, and ultimately, a poor overall sleep pattern.

Table 1
Baseline characteristics by obesity level based on the EASO framework

Characteristics	Total	Obesity level, No. (%)					
		Normal weight without morbidity	Normal weight with morbidity	EASO overweight	EASO new obesity	BMI obesity	*P* value
Number of participants	**N = 408453**	N = 56852	N = 77930	N = 157334	N = 17506	N = 98831	
Age, mean (SD), y	56.49 ± 8.07	53.73 ± 8.00	56.95 ± 8.08	57.16 ± 8.00	55.38 ± 8.18	56.85 ± 7.86	< .001
Sex, Male	224220 (54.89)	40097 (70.53)	48993 (62.87)	70452 (44.78)	12683 (72.45)	51995 (52.61)	< .001
Ethnicity White	388736 (95.17)	54661 (96.15)	74044 (95.01)	149662 (95.12)	16821 (96.09)	93548 (94.65)	< .001
Townsend deprivation index, mean(SD)	-1.43 ± 3.02	-1.73 ± 2.84	-1.51 ± 3.00	-1.53 ± 2.96	-1.75 ± 2.83	-0.99 ± 3.19	< .001
Binge drinking	11149 (2.73)	677 (1.19)	2073 (2.66)	4794 (3.05)	318 (1.82)	3287 (3.33)	< .001
Smoking/Smoked	185054 (45.31)	21007 (36.95)	33899 (43.50)	74467 (47.33)	6937 (39.63)	48744 (49.32)	< .001
WHtR, Mean(SD)	0.54 ± 0.07	0.46 ± 0.04	0.47 ± 0.04	0.54 ± 0.04	0.48 ± 0.02	0.62 ± 0.06	< .001
Sleep duration							< .001
Mean (SD)	7.17 ± 1.09	7.21 ± 0.92	7.17 ± 1.08	7.18 ± 1.07	7.15 ± 1.04	7.13 ± 1.22	
Chronotype							< .001
morning person	256598 (62.82)	36992 (65.07)	49251 (63.20)	98785 (62.79)	10999 (62.83)	60571 (61.29)	
evening person	151855 (37.18)	19860 (34.93)	28679 (36.80)	58549 (37.21)	6507 (37.17)	38260 (38.71)	
Insomnia							< .001
Never/rarely/Sometimes	295051 (72.24)	44732 (78.68)	54847 (70.38)	115731 (73.56)	12269 (70.08)	67472 (68.27)	
Usually	113402 (27.76)	12120 (21.32)	23083 (29.62)	41603 (26.44)	5237 (29.92)	31359 (31.73)	
No Snoring	256289 (62.75)	44393 (78.09)	57218 (73.42)	93471 (59.41)	12273 (70.11)	48934 (49.51)	< .001
Daytime dozing							< .001
Never/rarely	311535 (76.27)	47089 (82.83)	60284 (77.36)	119681 (76.07)	13919 (79.51)	70562 (71.40)	

Abbreviations: SD, standard deviation; EASO, European Association for the Study of Obesity; WHtR, Waist-to-Height Ratio; BMI, Body Mass Index.

Characteristics	Total	Obesity level, No. (%)					
		Normal weight without morbidity	Normal weight with morbidity	EASO overweight	EASO new obesity	BMI obesity	*P* value
Sometimes/Often/All	96918 (23.73)	9763 (17.17)	17646 (22.64)	37653 (23.93)	3587 (20.49)	28269 (28.60)	
Sleep pattern							< .001
Healthy	72547 (17.76)	15822 (27.83)	15826 (20.31)	25982 (16.51)	3449 (19.70)	11468 (11.60)	
Intermediate	253364 (62.03)	34997 (61.56)	48598 (62.36)	99774 (63.42)	10973 (62.68)	59022 (59.72)	
Poor	82542 (20.21)	6033 (10.61)	13506 (17.33)	31578 (20.07)	3084 (17.62)	28341 (28.68)	

Abbreviations: SD, standard deviation; EASO, European Association for the Study of Obesity; WHtR, Waist-to-Height Ratio; BMI, Body Mass Index.

Independent Associations of Obesity Status with Mortality

Over a median follow-up of 13.02 years (Interquartile range,IQR, 12.21–13.94), there were 6 991 CVD deaths and 34 146 all-cause deaths. After full adjustment (Model 2), all categories of excess weight or obesity-related morbidity were associated with a significantly higher risk of both CVD and all-cause mortality (Table 2). The highest risk was observed in individuals with BMI-defined obesity (BMI ≥ 30 kg/m²), who had a hazard ratio (HR) of 3.53 (95% CI, 3.10–4.02) for CVD mortality and 1.71 (95% CI, 1.63–1.79) for all-cause mortality. Participants classified as obese by the new EASO definition also demonstrated elevated risks, with HRs of 1.73 (95% CI, 1.41–2.12) for CVD mortality and 1.14 (95% CI, 1.06–1.23) for all-cause mortality. The population attributable fraction (PAF) analysis indicated that BMI-defined obesity accounted for the largest proportion of preventable deaths, with PAFs of 66.3% and 34.7% for CVD and all-cause mortality, respectively.

Table 2
Associations of obesity level with cardiovascular mortality and All-cause mortality based on the EASO framework.

Characteristics	Cases (%)	Model 0[a]		Model 1[b]		Model 2[c]		PAF% (95% CI)
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
CVD mortality								
Normal weight without morbidity	255/56852 (0.45%)	1.00		1.00		1.00		
Normal weight with morbidity	1221/77930 (1.57%)	2.44 (2.13, 2.79)	< .0001	2.27 (1.98, 2.60)	< .0001	2.24 (1.96, 2.57)	< .0001	46.33 (39.91, 52.06)
EASO overweight	2726/157334 (1.73%)	2.28 (2.00, 2.59)	< .0001	2.18 (1.92, 2.48)	< .0001	2.14 (1.88, 2.44)	< .0001	48.84 (42.40, 54.57)
EASO new obesity	147/17506 (0.84%)	1.72 (1.41, 2.11)	< .0001	1.76 (1.43, 2.15)	< .0001	1.73 (1.41, 2.12)	< .0001	16.11 (9.58, 22.16)
BMI obesity	2642/98831 (2.67%)	3.99 (3.51, 4.54)	< .0001	3.66 (3.22, 4.17)	< .0001	3.53 (3.10, 4.02)	< .0001	66.31 (62.08, 70.07)
All-cause mortality								
Normal weight without morbidity	2389/56852 (4.20%)	1.00		1.00		1.00		
Normal weight with morbidity	6668/77930 (8.56%)	1.50 (1.43, 1.57)	< .0001	1.42 (1.35, 1.49)	< .0001	1.41 (1.34, 1.47)	< .0001	20.74 (18.02, 23.38)
EASO overweight	13338/157334 (8.48%)	1.34 (1.28, 1.40)	< .0001	1.28 (1.23, 1.34)	< .0001	1.26 (1.21, 1.32)	< .0001	18.24 (15.19, 21.19)
EASO new obesity	940/17506 (5.37%)	1.15 (1.06, 1.24)	0.0004	1.16 (1.07, 1.25)	0.0002	1.14 (1.06, 1.23)	0.0005	3.62 (1.57, 5.63)
BMI obesity	10811/98831 (10.94%)	1.90 (1.82, 1.99)	< .0001	1.76 (1.68, 1.84)	< .0001	1.71 (1.63, 1.79)	< .0001	34.74 (32.34, 37.05)

Abbreviations: HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction; CVD, cardiovascular disease;

[a]Model 0 adjusted for age and sex.

[b]Model 1 additionally adjusted for ethnicity, Townsend deprivation index, binge drinking, and smoking status.

[c]Model 2 adjusted for terms in model 1 and sleep pattern.

Joint Association of Obesity Status and Sleep Patterns with Mortality

We next examined the combined effects of obesity and sleep patterns on mortality (Table 3; **Supplementary Fig S2**). A clear dose-response relationship was evident: mortality risk increased progressively with worsening obesity status and poorer sleep patterns. The highest risk was observed among individuals with BMI-defined obesity and a poor sleep pattern; compared to the reference group (normal weight without morbidity and healthy sleep), their HR for CVD mortality was 3.99 (95% CI, 3.07–5.19) and for all-cause mortality was 1.89 (95% CI, 1.73–2.06).

Table 3
Combined effects of obesity level, Sleep pattern, and the risk of cardiovascular mortality and all-cause mortality

Characteristics	Sleep pattern (HR, 95% CI)[a]			RERI[b]		*P* value for interaction
	Healthy	Intermediate	Poor	Intermediate	Poor	
CVD mortality						
Normal weight without morbidity	1.00	0.88 (0.65, 1.19)	1.30 (0.89, 1.90)			0.0942
Normal weight with morbidity	1.96 (1.46, 2.61)	2.15 (1.65, 2.80)	2.55 (1.93, 3.37)	0.30 (-0.08, 0.69)	0.29 (-0.29, 0.88)	
EASO overweight	1.89 (1.44, 2.49)	2.04 (1.58, 2.64)	2.44 (1.87, 3.18)	0.27 (-0.05, 0.58)	0.25 (-0.24, 0.73)	
EASO new obesity	1.68 (1.06, 2.66)	1.40 (1.00, 1.97)	2.67 (1.81, 3.94)	-0.15 (-0.94, 0.64)	0.75 (-0.37, 1.86)	
BMI obesity	3.26 (2.46, 4.32)	3.36 (2.59, 4.35)	3.99 (3.07, 5.19)	0.22 (-0.27, 0.72)	0.44 (-0.20, 1.09)	
All-cause mortality						0.1706
Normal weight without morbidity	1.00	0.93 (0.84, 1.02)	1.10 (0.97, 1.26)			
Normal weight with morbidity	1.23 (1.12, 1.37)	1.35 (1.24, 1.48)	1.59 (1.44, 1.75)	**0.19 (0.07, 0.30)**	**0.22 (0.05, 0.39)**	
EASO overweight	1.15 (1.05, 1.27)	1.23 (1.13, 1.33)	1.36 (1.24, 1.48)	0.15 (0.05, 0.25)	0.11 (-0.04, 0.26)	
EASO new obesity	1.08 (0.91, 1.28)	1.07 (0.96, 1.20)	1.30 (1.11, 1.53)	0.06 (-0.14, 0.27)	0.12 (-0.16, 0.40)	

Abbreviations: HR, hazard ratio; CI, confidence interval; RERI, relative excess risk due to interaction; CVD, cardiovascular disease.

[a]All results were calculated adjusted by age, sex, ethnicity, Townsend deprivation index, binge drinking, and smoking status.

[b]The estimates of RERI were calculated based on the reference group with Normal weight without morbidity and healthy sleep pattern.

[c]Likelihood tests was applied to test the significance of interaction term by comparing the model with and without the interaction term.

[*]*P* value < 0.05

Characteristics	Sleep pattern (HR, 95% CI)[a]			RERI[b]		*P* value for interaction
	Healthy	Intermediate	Poor	Intermediate	Poor	
CVD mortality						
BMI obesity	1.51 (1.36, 1.67)	1.65 (1.51, 1.79)	1.89 (1.73, 2.06)	**0.21 (0.08, 0.34)**	**0.28 (0.10, 0.45)**	

Abbreviations: HR, hazard ratio; CI, confidence interval; RERI, relative excess risk due to interaction; CVD, cardiovascular disease.

[a]All results were calculated adjusted by age, sex, ethnicity, Townsend deprivation index, binge drinking, and smoking status.

[b]The estimates of RERI were calculated based on the reference group with Normal weight without morbidity and healthy sleep pattern.

[c]Likelihood tests was applied to test the significance of interaction term by comparing the model with and without the interaction term.

[*]*P* value < 0.05

Further analysis revealed a significant additive interaction between sleep patterns and certain obesity statuses for all-cause mortality. Specifically, the joint effect of poor sleep combined with either “normal weight with morbidity” or “BMI-defined obesity” was greater than the sum of their individual effects, suggesting a synergistic relationship.

Mediation by Sleep in the Obesity-Mortality Association

Mediation analysis was conducted to determine the extent to which the association between obesity levels and mortality was mediated by sleep pattern (poor vs. healthy). The results, detailed in Table 4, show that poor sleep was a significant mediator for the effect of nearly all obesity categories on both mortality outcomes. For cardiovascular mortality, the proportion of risk mediated by poor sleep ranged from 4.4% (95% CI, 2.2%–8.8%) for “Normal weight with morbidity” to 6.9% (95% CI, 3.7%–12.4%) for “EASO overweight”. The mediating effect of poor sleep was substantially greater for all-cause mortality, explaining up to 15.9% (95% CI, 9.2%–26.1%) of the mortality risk associated with being in the “EASO overweight” category.

Table 4
Proportion of the association between obesity level and mortality risk mediated by sleep pattern

Characteristics	Poor vs. healthy sleep pattern	
	Mediation proportion (95% CI)[a]	*P* value
CVD mortality		
Normal weight without morbidity		
Normal weight with morbidity	4.4% (2.2% – 8.8%)	0.0012
EASO overweight	6.9% (3.7% – 12.4%)	< 0.001
EASO new obesity	6.8% (2.5% – 17.1%)	0.0140
BMI obesity	6.2% (3.4% – 11.2%)	0.0004
All-cause mortality		
Normal weight without morbidity		
Normal weight with morbidity	7.5% (4.8% – 11.7%)	< 0.001
EASO overweight	15.9% (9.2% – 26.1%)	< 0.001
EASO new obesity	15.5% (4.4% – 42.6%)	0.0069
BMI obesity	13.3% (9.7% – 18.0%)	< 0.001
Abbreviations: CI, confidence interval; CVD, cardiovascular disease.		
[a]Adjusted for age, sex, ethnicity, Townsend deprivation index, binge drinking, smoking status.		

Subgroup and Sensitivity Analyses

Subgroup analyses revealed varying patterns of effect modification by mortality outcome (**Supplementary Fig S3–S4**). For cardiovascular mortality, only smoking status significantly modified the association with obesity (P for interaction < 0.001). However, for all-cause mortality, significant interactions were observed for age, binge drinking, ethnicity, sex, and smoking status, indicating that the obesity-mortality association was not uniform across these subgroups. In sensitivity analyses, the main findings remained robust after excluding participants who experienced an event within the first year of follow-up, which mitigates the potential for reverse causation (Table 5).

Table 5

Sensitivity Analyses of Association Between obesity level and cardiovascular and all-cause mortality

Characteristics	Cardiovascular mortality		All-cause mortality	
	HR (95% CI)[a]	*P* value	HR (95% CI)[a]	*P* value
Obesity level[b]				
Normal weight without morbidity	1 [Reference]		1 [Reference]	
Normal weight with morbidity	2.30 (2.01, 2.64)	< .0001	1.41 (1.35, 1.48)	< .0001
EASO overweight	2.19 (1.92, 2.50)	< .0001	1.29 (1.23, 1.34)	< .0001
EASO new obesity	1.79 (1.46, 2.20)	< .0001	1.16 (1.07, 1.25)	0.0002
BMI obesity	3.70 (3.24, 4.22)	< .0001	1.76 (1.68, 1.84)	< .0001

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease;.

[a]Adjusted for age, sex, race and ethnicity, Townsend deprivation index, binge drinking, smoking status.

[b]In sensitivity analysis, participants with events occurring within the first year of follow-up were excluded to reduce potential reverse causation.

Discussion

This study elucidates the complex interplay between obesity, sleep patterns, and mortality, offering three pivotal insights. First, it underscores the complementary value of the novel EASO framework alongside the conventional BMI classification for risk stratification. Second, it quantifies the significant mediating role of sleep in the obesity-mortality pathway, repositioning sleep as a core biological regulator rather than a mere lifestyle factor. Third, it reveals a potent synergistic effect between obesity and poor sleep, which collectively amplify mortality risk. These findings collectively advocate for a more integrated and holistic approach to cardiometabolic health and mortality prevention.

Obesity is a well-established risk factor for both cardiovascular diseases and all-cause mortality (3, 23, 24). In our study, obesity levels defined by both the traditional BMI classification system and the novel EASO framework showed significant associations with mortality risks. These findings reaffirm the detrimental impact of obesity on long-term health outcomes, irrespective of the classification method employed (4, 25). However, the magnitude of risk differed between the two systems. While BMI-defined obesity exhibited a stronger association and higher Population Attributable Fraction (PAF), the EASO framework offers a critical complementary perspective. By integrating clinical attributes such as fat distribution and metabolic complications, it moves beyond a simple measure of adiposity to better capture the heterogeneous nature of obesity-related health risks. This comprehensive approach is particularly valuable for identifying individuals at high risk who are missed by the BMI threshold alone, reinforcing its role as an essential supplement to, rather than a replacement for, the conventional BMI classification (26, 27).

In addition to obesity, adverse sleep patterns once again emerged as an independent determinant of mortality risks for cardiovascular and all-cause mortality in our study (10, 28). Disturbed sleep involving either short sleep duration (< 7 hours) and long sleep duration (≥ 9 hours), fragmented sleep, or poor sleep quality significantly amplified mortality risks (10, 29). These findings echo previous research suggesting that sleep dysfunction contributes to cardiovascular and metabolic dysregulation through inflammatory pathways, hormonal imbalances (e.g., leptin and ghrelin dysregulation), and increased oxidative stress (11, 29–31). Notably, the mediating proportion of sleep was calculated as 6.8%–6.9% in cardiovascular mortality and 15.5%–15.9% in all-cause mortality in this study, indicating its meaningful contribution to

obesity-related health outcomes. While sleep alone cannot fully explain the observed associations, these findings underline its critical role in the obesity-mortality pathway, reframing sleep as not merely a lifestyle factor but a key element in chronic disease progression.

The joint effects of obesity and sleep patterns, as analyzed in this study, reveal a striking interaction that exacerbates mortality risks. Individuals with both obesity and adverse sleep patterns demonstrated the highest risks for both cardiovascular and all-cause mortality, suggesting a synergistic effect between the two factors. Mechanistically, this interplay may be mediated through shared biological pathways such as chronic inflammation, oxidative stress, and neuroendocrine dysregulation (32, 33). For example, obesity-induced systemic inflammation could increase vulnerability to the negative impacts of poor sleep, while disrupted sleep may further impair energy metabolism and hormonal regulation in individuals with obesity, amplifying the health risks (9, 34). These findings indicate the necessity of incorporating sleep health into obesity management programs and vice versa. Treating these interdependent factors in isolation may result in suboptimal health outcomes.

These findings have profound implications for clinical practice, particularly in the realm of obesity prevention and management. The complementary nature of the EASO framework underscores the need for multidimensional obesity assessments that go beyond BMI and consider factors such as fat distribution, metabolic health, and behavioral risks, enabling personalized risk stratification (35, 36). Furthermore, given the significant role of sleep as both an independent and mediating factor, incorporating regular sleep health evaluations into routine clinical care is imperative. Multidisciplinary interventions targeting both obesity and sleep may yield substantial benefits for reducing mortality risks. For example, an integrated approach combining weight management strategies with behavioral sleep therapies has the potential to optimize outcomes for at-risk individuals. Ultimately, this study advocates for a holistic model of mortality prevention that addresses both physical and behavioral determinants of health.

The primary strengths of this study lie in its large-scale, prospective design using the UK Biobank cohort, which afforded robust statistical power due to the extensive follow-up and large number of observed mortality events. Furthermore, we employed a comprehensive assessment of exposures by utilizing dual obesity frameworks (BMI and EASO) and a multidimensional sleep score, coupled with rigorous statistical analyses to ensure the validity and robustness of our findings.

Despite these strengths, this study has several limitations. First, the observational study design precludes definitive causal inference, and although we adjusted for multiple confounders, residual confounding cannot be entirely excluded. Second, key exposures such as sleep patterns were self-reported and assessed only at baseline, introducing potential recall bias and precluding analysis of their dynamic changes over time (37). Third, participants recruited in the UK Biobank might result in healthy volunteer bias (38).

Future research should leverage objective, longitudinal measures (e.g., actigraphy) to validate these findings (39, 40). Finally, the study cohort was predominantly White British, which may limit the generalizability of our findings to other ethnicities.

Conclusions

In conclusion, our study demonstrates that a comprehensive risk assessment integrating both advanced obesity classifications and sleep patterns is superior to traditional, single-factor approaches for predicting mortality. The EASO framework provides critical, complementary information to BMI, while poor sleep acts as both a powerful independent risk factor and a key mediator of obesity's lethal effects. The synergistic impact of co-existing obesity and poor sleep underscores the urgent need for a paradigm shift in clinical practice, moving from siloed management to an integrated

care model. Intervening on sleep health is not merely an adjunctive therapy but a direct and necessary strategy to mitigate obesity-related mortality.

Declarations

Competing Interests

None declared

Use of artificial intelligence (AI) tools

The authors used artificial intelligence tools solely to assist with literature search and verification of reference citations during the preparation of this manuscript. All content, analysis, and conclusions in the manuscript are the original work of the authors, and the AI tools were not used to generate any core research content or text.

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Authors' contributions

XJY, KZ and SW completed the conception and design of this research, as well as the analysis and interpretation of the data. KZ and SW completed the exploration of this research and the writing of the article, Other authors critical revision for important intellectual content. All authors read and approved the final manuscript.

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Data availability

The dataset(s) supporting the conclusions of this article is(are) available in the [https://www.ukbiobank.ac.uk/about-us/how-we-work/access-to-ukbiobank-data/], but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of UK Biobank. Reasonable requests should be directed to the UK Biobank management team.

Ethics approval

The project has approval from the North West Multi-centre Research Ethics Committee (MREC) (REC reference: 21/NW/0157), and it complies with the Helsinki Declaration. All the questionnaire surveys and data collection have been conducted with the written informed consent of each participant.

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