



Socioeconomic inequalities in developing cardiometabolic diseases and transition to depression: A trajectory analysis of large-scale population-based study

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ABSTRACT

Existing evidence demonstrates a high risk of developing depression in patients with cardiometabolic diseases (CMDs). However, it remains unclear whether socioeconomic inequality exacerbates the progression. We aimed to quantify the role of socioeconomic status (SES) in the progression from healthy to CMDs and their transitions to depression. A total of 376 610 participants (age 37–73 years) free from CMDs of interest, including type 2 diabetes (T2D), coronary heart disease (CHD) and stroke, from the ongoing UK Biobank study between 2006 and 2010 were included at baseline. Potential various SES groups were derived from latent class analysis using family income level, employment status and education attainment. In latent class analysis, three distinctive levels of SES (low, medium, and high) were identified. During the 15-year follow-up, we found significant associations were found between low SES and different progression stages of CMDs. In multivariate models, the hazard ratios (95 % confidence intervals) for low SES vs. high SES were 1.62 (1.53–1.71), 1.23 (1.17–1.29) and 1.25 (1.13–1.38) for transitions from healthy to T2D, CHD and stroke, and 2.17 (2.03–2.30), 1.63 (1.30–2.03), 1.62 (1.30–2.03), 1.70 (1.11–2.60) for risk of transition to depression from healthy, T2D, CHD and stroke, respectively. Socioeconomic inequalities were associated with almost all transition stages from healthy to CMDs, subsequently to depression, with different magnitude of associations. These findings support the need for targeted screening programs for depression in CMD patients, and policy interventions addressing socioeconomic inequalities through improved access to healthcare, education, and economic opportunities for disadvantaged populations.

1. Introduction

Both physical and mental disorders contribute significantly to the increasing burden on health care systems worldwide (GBD, 2019 Diseases and Injuries Collaborators, 2020; GBD, 2019 Mental Disorders Collaborators, 2022). Cardiometabolic diseases (CMDs), primarily comprising type 2 diabetes (T2D), coronary heart disease (CHD), and stroke, are the leading causes of disability and mortality globally (GBD, 2017 Risk Factor Collaborators, 2018). Meanwhile, mental disorders represent the third leading cause of disease burden, with depression accounting for 37 % of all years of life lost to disability (GBD, 2019 Mental Disorders Collaborators, 2022).

The co-occurrence of CMDs and depression is well-documented and

clinically significant (Naylor C PM, 2012). The prevalence of major depression in patients with cardiovascular disease (CVD) has been estimated to be two to three times higher than in the general population (Hare et al., 2014). Among people living with T2D in the UK, the prevalence of depression increased from 29 % in 2006 to 43 % in 2017 (Dibato et al., 2022). As advances in medical treatment enable individuals with CMDs to live longer, understanding the subsequent development of depression in these patients becomes increasingly important for healthcare planning and patient care.

Socioeconomic status (SES) encompasses an individual's or family's social and economic position relative to others, typically measured through income, education, occupation, and related factors (Galea and Vaughan, 2019). Lower SES has been consistently associated with

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increased risk of developing individual CMDs. Existing evidence has reported that the associations between SES and risks of incident T2D and cardiovascular diseases (CVD) (Gabriel et al., 2021; Stringhini et al., 2013; Zhang et al., 2021). Similarly, Mendelian randomization studies have established causal links between socioeconomic disadvantage and increased risk of developing depression (Cai et al., 2022; Wray et al., 2018).

The relationship between CMDs and subsequent depression incidence has important clinical implications. Large prospective studies have documented that individuals who develop coronary events or receive a diabetes diagnosis face significantly elevated risk of developing new-onset depression, even after accounting for shared risk factors (Semenkovich et al., 2015). Furthermore, depression that develops following CMD diagnosis is associated with worse clinical outcomes, including increased cardiovascular events, poorer glycemic control, and higher mortality rates (Qiao et al., 2021). A recent meta-analysis of 39 studies reported an overall prevalence of depression in CVD patients of 20.8 % (Zeng et al., 2025). These findings suggest that socioeconomic inequalities may influence not only the initial development of CMDs but also the subsequent transition from CMD to depression.

Despite growing recognition of these relationships, critical gaps remain in our understanding. First, previous studies only focused on the impact of socioeconomic inequalities on one of these transitions (mainly from health to single CMD), and none have evaluated the potential effects of SES on the development and prognosis of CMDs. The investigation on the effect of SES in CMDs trajectory would be critical for evidence-based prevention and health policy. Second, most existing research relies on single SES indicators (income alone, education alone, or occupation alone), which may inadequately capture the multidimensional nature of socioeconomic position (Petrovic et al., 2018; Quaglia et al., 2013). Therefore, it's necessary to establish a comprehensive socioeconomic parameter consisting of different aspects of the SES.

To address these gaps, this study uses multistate models to investigate the differential impact of comprehensive SES measures on the complete disease trajectory in the UK Biobank. Specifically, we examine: (1) the transition from disease-free state to incident CMD (T2D, CHD, or stroke); (2) the subsequent development of incident depression following CMD diagnosis; and (3) transitions to death from each disease state.

2. Materials and methods

2.1. Study population and design

This was a prospective, population-based cohort study of participants enrolled in the UK Biobank cohort. Between April 2006 and December 2010, the UK Biobank recruited over half a million adults (37–73 years old) from the general population. Participants attended one of 22 assessment centers across England, Scotland, and Wales, where they completed nurse-led electronic questionnaires, physical examination and biological samples collections, and agreed to be followed for multiple health-related outcomes (Sudlow et al., 2015). Among the 502 411 participants of initial sample, we excluded participants with prevalent T2D, CHD, stroke or depression at baseline; missing information on covariates; who didn't provide information on family income level, employment status, and education level; who recorded on the same date of diseases and death; who requested to be removed from the UK Biobank dataset during the 15 years of follow-up (Supplemental Figure S1). All participants provided informed consent through electronic signature. UK Biobank was approved by the Northwest Multi-Centre Research Ethics Committee (Reference 11/NW/03820) as a Research Tissue Bank.

2.2. Assessment of socioeconomic status

Self-reported family income level, employment status, and education attainment were used to reflect different aspects of SES according to the previous study (Zhang et al., 2021). Family income level of participants was recorded via a touchscreen questionnaire at baseline: "What is the average total income before tax received by your HOUSEHOLD?" Participants could choose an option from <£18 000, £18 000 to £30 999, £31 000 to £51 999, £52 000 to £100 000, >£100 000, do not know, or prefer not to answer. Employment status was recorded as in paid employment or self-employed, retired, doing unpaid or voluntary work, full or part-time student, looking after home and/or family, unable to work because of sickness or disability, unemployed, none of the above, or prefer not to answer. Those who chose the first four options were regrouped into "employed" group and others (except for the last two options, which were treated as missing values) were grouped into the "unemployed" group. Education attainment was asked by the following question: "Which of the following qualifications do you have? (You can select more than one)" Participants could choose the answers as college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ, HND, HNC or equivalent, other professional qualifications, none of the above (equivalent to less than high school diploma), or prefer not to answer (which was excluded from our analyses as missing values). Those who chose the first option was grouped into the "college or above" group, and those who chose the last option was grouped into the "less than high school" group, while others were grouped into the "less than high school" group (Zhang et al., 2021).

An overall SES parameter was created using latent class analysis (LCA) based on family income level, employment status, and education attainment. LCA is a statistical model, allowing all participants classified into mutually exclusive potential categorizes without omission based on a set of observed variables in the model (Lanza and Collins, 2008). LCA was conducted using "poLCA" package in the R software, and three latent classes were identified in the present study, which respectively represented a high, medium, and low SES according to the item-response probabilities. Detail information on the assessment of LCA was seen in **Supplementary Methods**.

To validate our findings and examine whether the associations persist using an alternative measure of socioeconomic position, we conducted a sensitivity analysis using the Townsend Deprivation Index (TDI) instead of our primary individual-level SES measure. TDI is an area-level measure of socioeconomic deprivation assigned based on participants' postal codes at baseline. It is derived from census data incorporating four variables: unemployment, non-car ownership, non-home ownership, and household overcrowding. TDI scores are provided as a continuous measure, with higher values indicating greater area-level deprivation (Peter Townsend PP, 1988).

2.3. Ascertainment of outcome

All residents in England, Scotland, and Wales have a unique National Health Service (NHS) identification number, which were used for linking all participants to hospital admission electronic records or in death register databases. CMDs defined in the current study included CHD, T2D, and stroke. Incidence of the single CMD was ascertained by the International Classification of Disease version 10 (ICD-10): codes for T2D (E11; Shubrook, 2017), CHD (I20-25; Daniel Z L Chan, 2024) and stroke (I60-61, I63-64; Hsieh et al., 2020). Depression cases were defined using ICD-10 codes F32-33 (Fiest et al., 2014). Death information was obtained via linking to national death registries. Participants were considered at risk from enrolment to death, loss to follow-up, or the end of the follow-up (30 September 2021), whichever came first. Detailed information about the linkage procedures can be found at <http://content.digital.nhs.uk/services>.

2.4. Assessment of covariates

Potential confounding variables were selected based on previous theory and literature and obtained through questionnaires at baseline assessment, including age (calculated at baseline assessment centers), sex (female, male), ethnicity (White, non-White), body mass index (BMI, calculated as weight divided by the square of height, kg/m^2), self-reported smoking status (never, previous, current), drinking status (never, previous, current), physical activity (low, moderate, high), self-rated health status (excellent, good, fair, poor), and diet pattern (unhealthy or healthy). Self-rated health status was obtained through questionnaire at baseline. Participants were asked: “In general how would you rate your overall health”, and then chose an option from excellent, good, fair, poor, do not know, or prefer not to answer. A cumulative diet score was constructed to reflect the diet pattern according to previous studies (Morris et al., 2015; Mozaffarian, 2016). Briefly, a total of 7 food items were used to create the diet score, including the frequency of consumption of fruits, vegetables, fish, processed meat, unprocessed red meat, whole grains, and refined grains. The healthy standards for each dietary component were listed as: (1) fruits: ≥ 3 servings/day; (2) vegetables: ≥ 3 servings/day; (3) fish: ≥ 2 servings/week; (4) processed meat: ≤ 1 serving/week; (5) unprocessed red meat: ≤ 1.5 servings/week; (6) whole grains: ≥ 3 servings/day; (7) refined grains: ≤ 1.5 servings/day. We assigned 1 point for a healthy level and 0 point for an unhealthy level. Finally, a diet score ranging from 0 (least healthy) to 7 (healthiest) was derived by summing the points, with ≥ 4 scores indicating a healthy diet pattern.

2.5. Statistical analysis

We summarized baseline characteristics by SES using descriptive statistics, reporting the mean and standard deviation (SD) of continuous variables, and proportions for categorical variables.

Multi-state model was performed to assess the role of SES in the temporal progression from free of CMD to CHD, T2D and stroke, then transition to depression, and subsequently to death (Fig. 1) (Putter et al., 2007). Multi-state model is an extension of competing risk model, which helps to explore how some factors affect different stages of the disease progression (Han et al., 2021). Twelve transitions were finally included in the multi-state model: (1) from healthy to T2D, (2) from healthy to

CHD, (3) from healthy to stroke, (4) from healthy to depression, (5) from healthy to death, (6) from T2D to depression, (7) from CHD to depression, (8) from stroke to depression, (9) from T2D to death, (10) from CHD to death, (11) from stroke to death, and (12) from depression to death. In each transition path, Cox proportional hazards models were fitted to estimate the hazard ratios (HRs) and 95 % confidence intervals (CIs). All models were adjusted for age, sex, ethnicity, BMI, smoking status, alcohol status, diet pattern, physical activity and self-rated health status. The reference group was set as the participants with high SES level. For participants who entered different states on the same date, we theoretically calculate the entry date of the prior state as the entry date of the latter state minus 1 day. For example, for participants who died of CMD, the date of occurrence of the first CMD is equal to the date of death minus 1 day.

We also used the multi-state model with the same setting to analyze the effects of SES on different pathways from baseline to any of CMDs, then to cardiometabolic multimorbidity (CMM), subsequently to depression, and to the absorbing state—death (Supplementary Figure 2), and nine transitions were resulted. In this pattern, CMM was defined as having two of three individual CMDs (T2D, CHD and stroke).

For the transition from CMDs to depression, subgroup analyses were conducted to evaluate the potential effect modifications by the potential risk factors: age groups (<60 and ≥ 60 years), sex (female and male), smoking status (never, ever), physical activity (inactive and active), diet pattern (unhealthy and healthy), BMI ($<25 \text{ kg}/\text{m}^2$ and $\geq 25 \text{ kg}/\text{m}^2$), and self-rated health status (good and bad).

Several sensitivity analyses were performed to confirm the robustness of our results. First, to alleviate the potential misclassification bias that depression cases might not totally be recorded in hospital inpatient records, the Patient Health Questionnaire (PHQ)-9 questionnaire was used to measure and identify depression. PHQ-9 that was surveyed in 2016 is a nine-item questionnaire which scores each of the nine DSM-IV criteria for depression as 0 (not at all) to 3 (nearly every day) with a total score ranging from 0 to 27, and score of 10 or higher is indicative of depression symptom (Levis et al., 2019). The PHQ-9 has shown good sensitivity and specificity for the diagnosis of depression in a variety of populations (Levis et al., 2020). Thus, we used logistic regression models to examine the association between SES and depression among participants with prevalent CMDs at baseline. Second, given the impact of cancer history on depression, we repeated the analysis after excluding

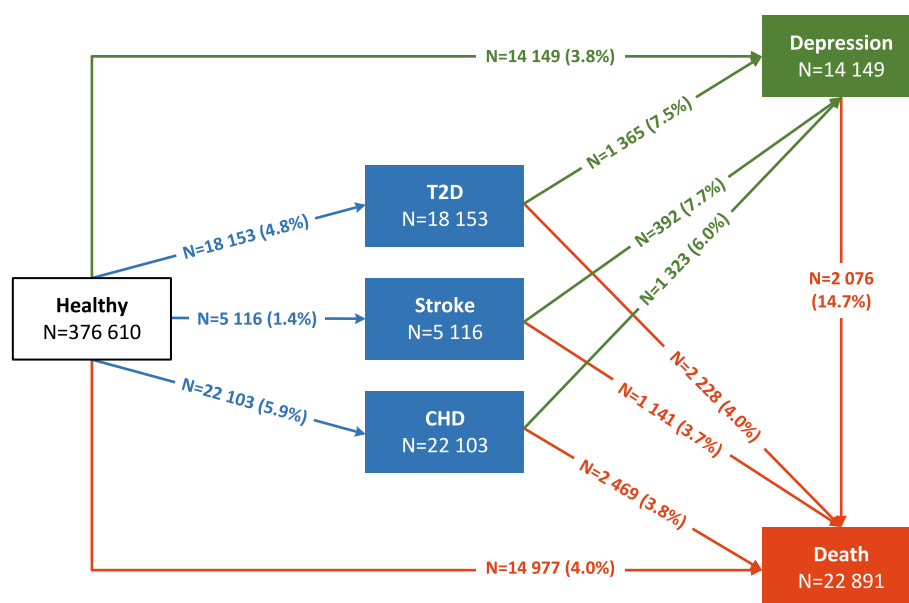


Fig. 1. Numbers (percentages) of participants in transition from baseline to one of T2D, CHD and stroke, then to depression, and subsequently to death. Abbreviations: T2D type 2 diabetes, CHD coronary heart disease.

participants with prevalent cancer at baseline. Third, we tried another two different analytical strategies to further examine the influence of patients who reached multiple disease states on the same day as previous published study (Luo et al., 2022), including 1) calculating the entry date of the prior state using additional four different time intervals instead of 1 day, i.e., 0.5 year, 1 year, 3 years and 5 years; 2) excluding participants who entered different states on the same date. Fourth, we also excluded participants with CMDs diagnosed within two years since enrollment to avoid the potential reverse causation.

All analyses were conducted using R software (version 4.2.0), and all *P* values were two-sided. Multi-state model was conducted using “mstate” package in the R software.

3. Results

3.1. Descriptive analysis

Table 1 shows the baseline characteristics of the study populations according to SES. A total of 376 610 participants free of CMDs and depression were finally included in the main analyses, 54.0 % were female and the mean age was 55.9 years. 68 619 (18.2 %) participants were categorized as high SES group, 212 778 (56.0 %) in the medium SES group, and 95 213 (25.3 %) in the low SES group by LCA method. Participants with low SES level were more likely to be female, with a

higher BMI, be previous or current smokers, be never or previous drinkers, with high physical activity, with fair or poor self-rated health, had an unhealthy diet pattern.

During a maximum follow-up of 15 years, 18 153 (4.8 %) participants developed T2D, 22 103 (5.9 %) participants developed CHD, 5116 (1.4 %) developed stroke. 14 149 (3.8 %) participants developed depression without experiencing any of CMDs, 3080 (7.5 %) individuals were diagnosed with depression after development of CMDs. 7914 participants died after diagnosed with CHD, T2D, stroke or depression, 14 977 died without experiencing CMDs or depression. Compared with participants who were diagnosed with CHD, T2D, or stroke, participants with depression were more likely to die afterwards, with 2076 (14.7 %) died during follow-up (Fig. 1).

Supplementary Fig. 2 shows another transition pattern (baseline → CMDs → CMM → depression → death). Of the 45 372 incident CMD patients, 5690 developed CMM, then 403 developed depression, after which 2076 died. 14 977 participants died without experiencing CMD or depression.

3.2. Multi-state analysis

The transition probability curves in Fig. 2 present multiple possible state transitions and corresponding probabilities over the 14 years. At the longest follow-up of 14 years, given the average level of covariates in

Table 1

Baseline characteristics of participants according to socioeconomic status.

Characteristics	Total (N = 376 610)	Socioeconomic status			P value
		High (N = 68 619)	Medium (N = 212 778)	Low (N = 95 213)	
Age, Mean (SD)	55.9 (8.1)	52.4 (7.2)	55.4 (8.0)	59.4 (7.5)	<0.001
Female	203 416 (54.0)	33 787 (49.2)	113 056 (53.1)	56 573 (59.4)	<0.001
Household income (£)					<0.001
Less than 18 000	76 651 (20.4)	0 (0.0)	0 (0.0)	76 651 (80.5)	
18 000–30 999	94 685 (25.1)	0 (0.0)	77 025 (36.2)	17 660 (18.5)	
31 000–51 999	101 719 (27.0)	944 (1.4)	100 416 (47.2)	359 (0.4)	
52 000–100 000	81 566 (21.7)	46 055 (67.1)	35 337 (16.6)	174 (0.2)	
Greater than 100 000	21 989 (5.8)	21 620 (31.5)	0 (0.0)	369 (0.4)	
Qualification					<0.001
Less than high school	49 815 (13.2)	0 (0.0)	8789 (4.1)	41 026 (43.1)	
High school or equivalent	189 236 (50.2)	6910 (10.1)	141 273 (66.4)	41 053 (43.1)	
College or above	137 559 (36.5)	61 709 (89.9)	62 716 (29.5)	13 134 (13.8)	
Employment					<0.001
Unemployed	21 437 (5.7)	4468 (6.5)	1851 (0.9)	15 118 (15.9)	
Employed	355 173 (94.3)	64 151 (93.5)	210 927 (99.1)	80 095 (84.1)	
Ethnicity					<0.001
White	338 352 (89.8)	59 889 (87.3)	193 197 (90.8)	85 266 (89.6)	
Other	38 258 (10.2)	8730 (12.7)	19 581 (9.2)	9947 (10.4)	
BMI, Mean (SD)	27.2 (4.7)	26.3 (4.2)	27.2 (4.6)	27.8 (5.0)	<0.001
Smoking status					<0.001
Never	209 496 (55.6)	43 144 (62.9)	120 087 (56.4)	46 265 (48.6)	
Previous	129 238 (34.3)	21 181 (30.9)	73 066 (34.3)	34 991 (36.8)	
Current	37 876 (10.1)	4294 (6.3)	19 625 (9.2)	13 957 (14.7)	
Alcohol status					<0.001
Never	13 126 (3.5)	1257 (1.8)	5986 (2.8)	5883 (6.2)	
Previous	11 563 (3.1)	1260 (1.8)	5224 (2.5)	5079 (5.3)	
Current	351 921 (93.4)	66 102 (96.3)	201 568 (94.7)	84 251 (88.5)	
Physical activity (IPAQ)					<0.001
Low	59 030 (15.7)	12 204 (17.8)	33 420 (15.7)	13 406 (14.1)	
Moderate	132 210 (35.1)	27 355 (39.9)	74 973 (35.2)	29 882 (31.4)	
High	130 067 (34.5)	22 617 (33.0)	74 206 (34.9)	33 244 (34.9)	
Missing	55 303 (14.7)	6443 (9.4)	30 179 (14.2)	18 681 (19.6)	
Self-rated health					<0.001
Excellent	69 228 (18.4)	19 164 (27.9)	38 905 (18.3)	11 159 (11.7)	
Good	225 441 (59.9)	40 403 (58.9)	132 433 (62.2)	52 605 (55.2)	
Fair	70 329 (18.7)	8152 (11.9)	37 210 (17.5)	24 967 (26.2)	
Poor	11 612 (3.1)	900 (1.3)	4230 (2.0)	6482 (6.8)	
Diet pattern					<0.001
Unhealthy	175 410 (46.6)	29 907 (43.6)	99 146 (46.6)	46 357 (48.7)	
Healthy	201 200 (53.4)	38 712 (56.4)	113 632 (53.4)	48 856 (51.3)	

Values are numbers (percentages) unless stated otherwise.

Abbreviations: *SES* socioeconomic status, *BMI* body mass index.

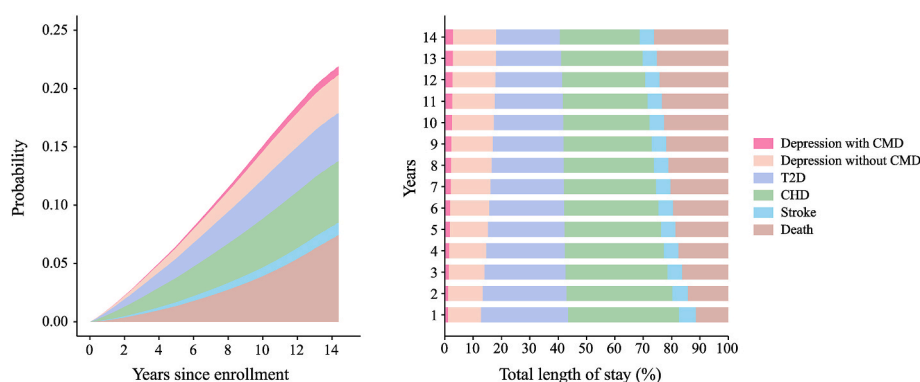


Fig. 2. Transition probability curves and estimated percentage of total length of stay for transition states over 14 years. Cardiometabolic diseases include T2D, CHD and stroke. All covariates were set to the average level of the UK Biobank population in the present analysis. Abbreviations: T2D type 2 diabetes, CHD coronary heart disease, CMD cardiometabolic disease.

the UK Biobank population, a healthy individual had 4.1 %, 5.3 %, and 1.1 % probabilities to develop T2D, CHD, and stroke, respectively, and had 0.7 % probabilities to develop depression after CMDs.

Multi-state models showed the differential role of SES in the temporal trajectories of developing one of T2D, CHD and stroke, then transition to depression, and ultimately to death (Fig. 3). We found that low SES compared to high SES was related to development of T2D, CHD and stroke, with HRs of 1.62 (95 % CI: 1.53–1.71), 1.23 (95 % CI: 1.17–1.29) and 1.25 (95 % CI: 1.13–1.38), respectively. Meanwhile, low SES was associated with higher risk of incident depression (HR = 2.17, 95 % CI: 2.03–2.30). Of note, low SES could also increase the risk of transition from first CMD to depression (HR [95 % CI] = 1.63 [1.30–2.05] for T2D; 1.62 [1.30–2.03] for CHD; 1.70 [1.11–2.60] for stroke).

When the cases of CMDs combined, similar results were observed in transition from CMDs to depression, the adjusted HRs (95 % CI) were 1.26 (1.08–1.47), 1.71 (1.46–2.01) for transitions from CMD to depression in medium SES level and low SES level, respectively (Supplementary Fig. 3).

3.3. Subgroup analyses

Subgroup analyses of the transition from CMDs to depression was assessed by age (<60 years and ≥60 years), sex (female and male), smoking status (never and ever), physical activity (inactive and active), diet pattern (unhealthy and healthy), BMI (<25 kg/m² and ≥25 kg/m²), and self-reported health status (good and bad). No statistically significant interactions were found among the above risk factors (*P* for interaction >0.05) (Fig. 4, Supplementary Table 1).

3.4. Sensitivity analyses

The robustness of our findings was confirmed by a series of sensitivity analyses. TDI was used in this study instead of family income level, employment status, and education attainment to explore the role of area-level SES in the multi-state models. In general, the associations between TDI and health outcomes were somewhat weaker compared with individual level SES (Supplementary Figure 4). The results were not substantially altered when redefining depression cases by using the PHQ-9 (Supplementary Table 2), excluding the participants with prevalent cancers at baseline (Supplementary Table 3), considering the influence of participants who were diagnosed with multiple CMDs on the same day with different time intervals (Supplementary Table 4), and excluding participants who entered different states on the same day (Supplementary Figure 5). Furthermore, while participants diagnosed with CHD, T2D and stroke cases within the first two years since enrollment were excluded, all associations remained robust

(Supplementary Figure 6).

4. Discussion

In this large prospective cohort study of 376 610 participants, we examined the impact of SES levels on the whole course in developing one of CHD, T2D and stroke, then transition to depression, and subsequently to death. We found that socioeconomic inequalities played important roles in multiple transition stages, including from healthy to CMDs, CMDs to depression, healthy or CMDs to death. Specifically, the effects of SES were strongest on the transitions from health to depression, followed by the transition from T2D to depression, and the transition from CHD to depression. In addition, we also quantified the cumulative probabilities of transitions from CMDs to depression and found that participants with low SES had an increased risk of post-CMDs depression. Furthermore, there were similar findings of effect modification among potential risk factors.

Our results both confirm and extend prior findings in important ways. The increased CMD risk among low SES individuals aligns with established evidence, including Zhang et al.'s (Zhang et al., 2021) demonstration of higher CVD incidence among disadvantaged populations and Kivimäki et al.'s finding that diabetes risk from occupational stressors was concentrated in low SES groups (Kivimäki et al., 2015). However, our study reveals that these initial disparities represent only the beginning of diverging health trajectories. The 20–40 % higher risk of progressing from CMD to depression among low SES individuals suggests that socioeconomic disadvantage not only increases disease incidence but also shapes post-diagnosis outcomes.

Mechanistically, our findings support a complex interplay between material, psychosocial, and behavioral pathways. While Foster et al. (2018) showed that unhealthy lifestyles partially mediate SES-health associations, Zhang et al. demonstrated that lifestyle factors explain only 4–12 % of socioeconomic health inequities (Zhang et al., 2021). Our results, showing persistent SES gradients after adjustment for health behaviors, reinforce that addressing lifestyle alone is insufficient.

The implications extend beyond individual risk factors to healthcare system responses. The pronounced SES gradient in CMD→depression transitions likely reflect differential access to integrated care, psychosocial support, and resources for managing chronic conditions. This aligns with global evidence from Avan et al. showing widening gaps in stroke outcomes between high and low-resource settings, despite overall improvements in stroke care (Avan et al., 2019). Our findings suggest that without targeted interventions addressing these systematic disparities, improvements in CMD treatment may paradoxically widen health inequalities by preferentially benefiting those with greater socioeconomic resources.

SES has been validated as a powerful predictor of morbidity and

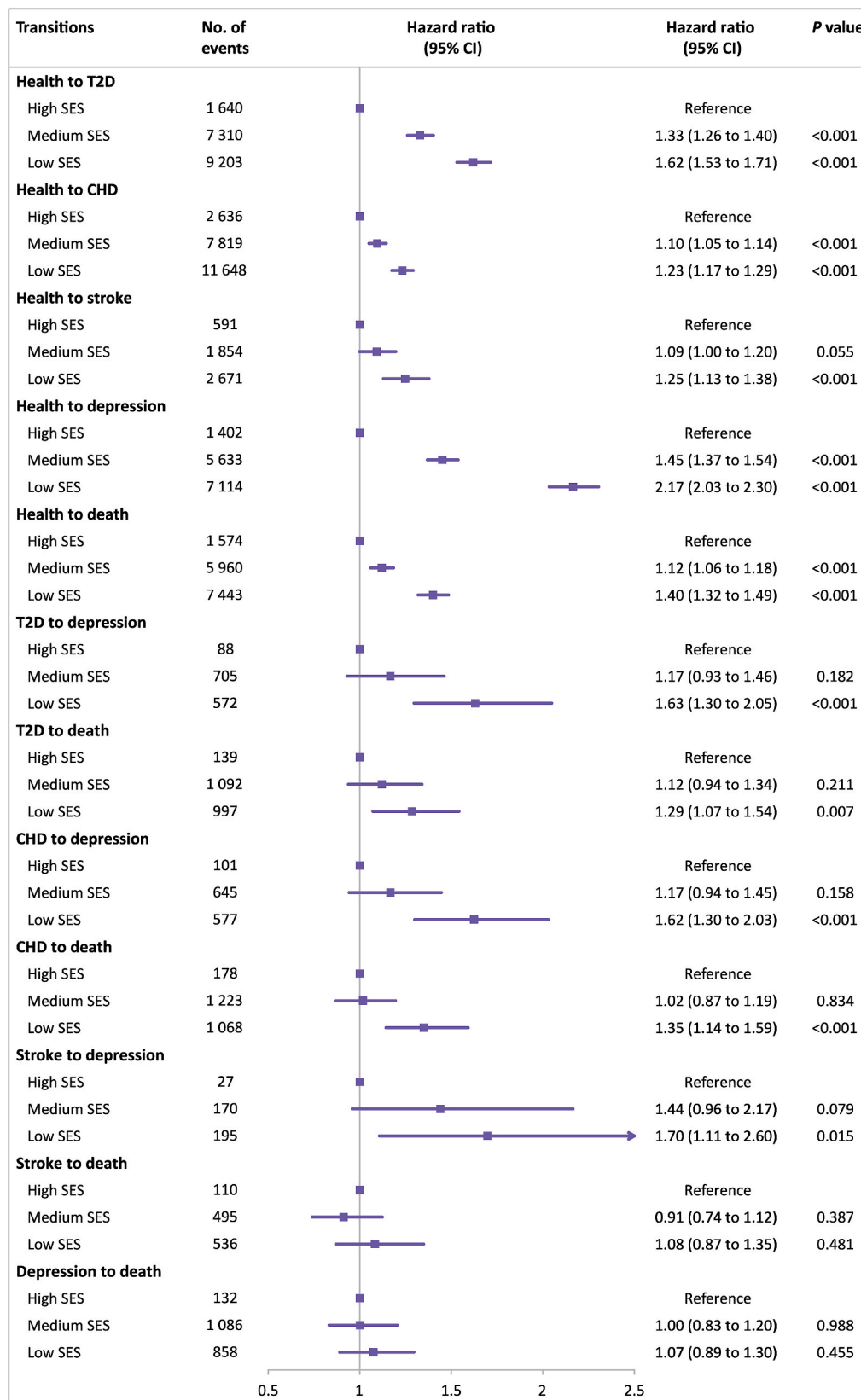


Fig. 3. Hazard ratios (95 % CI) for transitions from baseline to T2D, CHD or stroke, then to depression, and subsequently to death by SES. The number of events refers to number of cases with the corresponding exposure in each transition. The analyses were adjusted for age, sex, ethnicity, body mass index, smoking status, alcohol status, diet pattern, physical activity and self-rated health status. Abbreviations: *CI* confidence interval, *T2D* type 2 diabetes, *CHD* coronary heart disease, *SES* socioeconomic status.

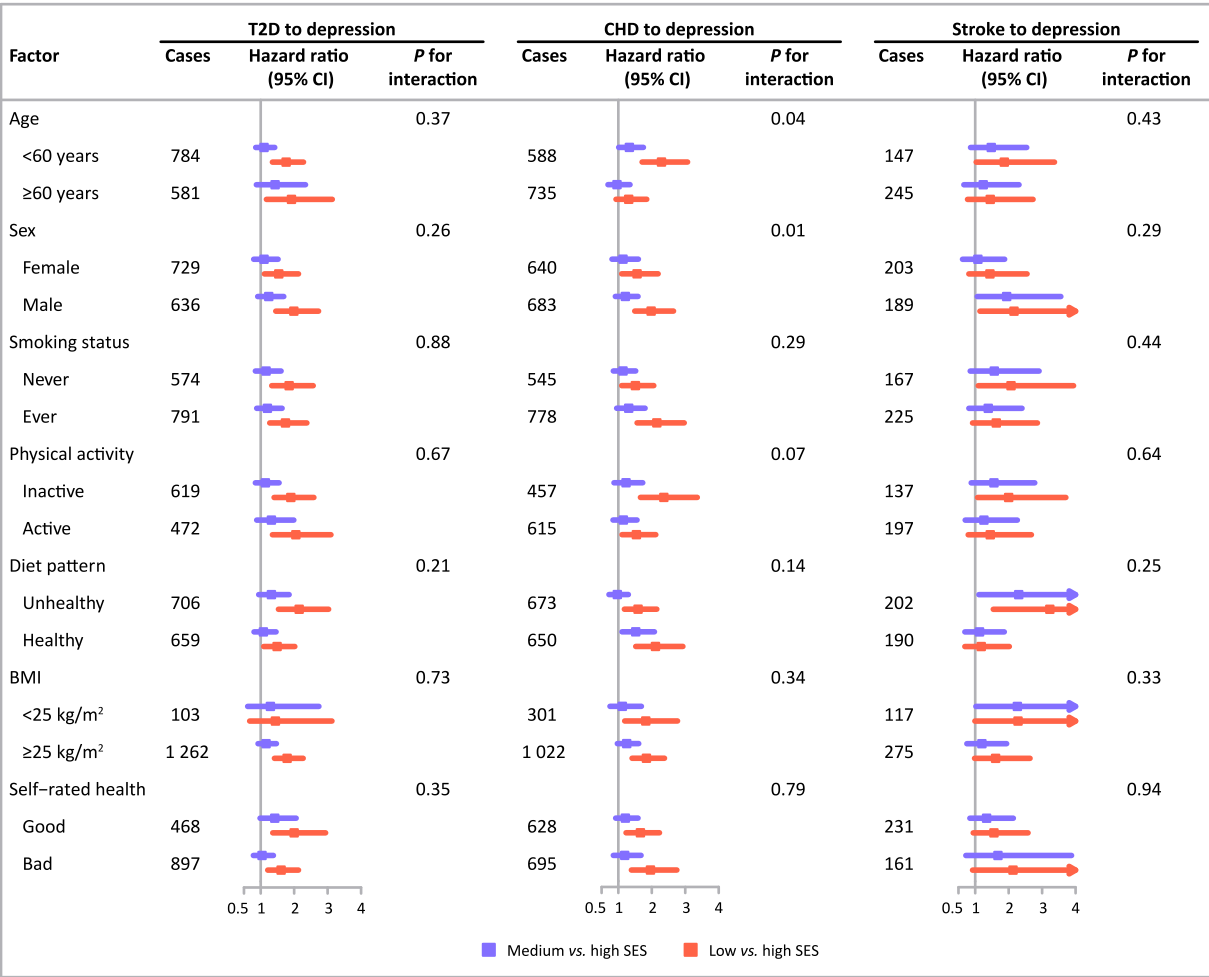


Fig. 4. The role of SES in the transitions from T2D, CHD and stroke to depression stratified by potential risk factors. The analyses were adjusted for age, sex, ethnicity, BMI, smoking status, alcohol status, diet pattern, physical activity and self-rated health status. Abbreviations: *SES* socioeconomic status, *T2D* type 2 diabetes, *CHD* coronary heart disease, *CI* confidence interval, *BMI* body mass index.

mortality, independent of lifestyle risk factors, and access to health care (Rawshani et al., 2015, 2016; Stringhini et al., 2017). Most previous studies only focused on associations of SES with single transition path, such as healthy to CMDs, healthy to depression. A prior study conducted among 443 999 US and UK populations revealed that disadvantage SES was associated with higher risks of incident CVD (Zhang et al.). Findings from UK Biobank study showed that the most deprived participants combined with the least healthy lifestyle had a 41 % higher risk of CVD incidence (Foster et al., 2018). Previous published meta-analysis consisted of 222 120 participants found that the association between long working hours and T2D was evident only in the low SES group (Kivimäki et al., 2015). The Australian Diabetes, Obesity and Lifestyle (AusDiab) study examined the role of area-level SES on the development of abnormal glucose metabolism (AGM), and found that people living in the most disadvantage areas were significantly more likely to develop AGM (Williams et al., 2012). An ecological analysis from the Global Burden of Disease study suggested that stroke incidence and mortality have declined globally since 2005, while an increase in stroke prevalence has only been observed in middle-income countries, and a significant decline in stroke mortality has been observed in wealthier countries (Avan et al., 2019). At the same time, there is increasing attention on the association of low SES with mental health (Agerbo et al., 2021; Han et al., 2018; Li et al., 2021), and MR study has provided robust evidence that SES play broad impacts on depression (Wray et al., 2018). In our study, using multiple SES construction indicators, we further demonstrated that socioeconomic inequalities were associated

with higher risk of incident T2D, CVD and depression. The above studies mainly focused on exploring the relationship of SES with occurrence with single CMD or depression. However, our study highlighted the new notion of the effects of socioeconomic inequities on different transition stages from healthy to single CMD, subsequently to depression, and then to death in a whole perspective of disease occurrence, progression and prognosis. Previous published studies have suggested that prevalence of various physical diseases could further increase the risk of depression. For instance, a recent meta-analysis concluded that stroke significantly increased the risk of depressive symptoms (Le et al., 2023). A previous study reported that prevalent CHD was associated with an increase in depression risk, and they shared environmental factors (Khandaker et al., 2020). A cross-sectional study of 391 083 UK Biobank participants found a dose-dependent relationship between the number of CMDs and depression risk, with odds ratios increasing from 1.26 for one CMD to 2.13 for three or more CMDs, adjusted for confounders (Gong et al., 2022). A review suggested an association between T2D and depression, but longitudinal research is needed to identify risk factors and mechanisms for depression in patients with diabetes (Moulton et al., 2015). Recently, the American Heart Association has issued a scientific statement suggesting that clinicians should routinely assess mental health for patients with CVD and individuals at risk for CVD (Levine et al., 2021). Thus, identifying risk factors of the progression from CMDs to depression is highly relevant to reducing disease burden. To the best of our knowledge, this study broadly extends previous work on this topic and fills the knowledge.

Our analysis confirmed the socioeconomic disparities in CMDs incidence and extended the findings to transition from CMDs to incidence of depression. A pooled analysis of individual data from 24 countries with different levels of SES, including Europe, the US, Latin America, Africa, and Asia, showed that the number of years of functioning lost due to adverse socioeconomic circumstances was comparable to or greater than that lost due to major risk factors for chronic diseases, such as insufficient physical activity, diabetes, obesity, and smoking (Stringhini et al., 2018). It's acknowledged that people with lower SES are less likely to receive good-quality acute hospital and rehabilitation care than people with higher SES (Marshall et al., 2015). Thus, exploring the possible methods to reduce socioeconomic inequity in health is urgently needed. Using the same analysis strategy as previous study (Zhang et al., 2021), we also compared the overall individual level SES and TDI in the UK Biobank and found that the associations of individual level SES with health outcomes were stronger than those of area level SES. This might be explained because postcode derived TDI reflects different aspects and has several limitations, such as inability to determine social causes of health, inability to distinguish individual differences, confound with other environmental health determinants, unreliability when populations are heterogeneous or change quickly, and inapplicability to mobile communities (Moscrop et al., 2020). Thus, it's highly important to construct an overall individual level SES variable including family income level, individual employment status, and education level.

4.1. Strengths and limitations

Our study has several strengths. Multi-state models were used to examine the role of SES in the development of CMDs and the transition to depression, and ultimately to death. This enabled us to explore the impacts of SES on different states of the disease progression from health to CMDs, subsequently to depression, and rule out the competing risk from death. The large-scale sample size from the UK Biobank allowed us to adjust for a considerable number of confounders that known to influence the relations of SES with transitions to multiple health outcomes and provided substantial power to further investigate all transitions of specific CMDs. Moreover, the level of SES was measured by individual and area perspective. We also constructed an overall individual's SES variable that consisted of income, occupation, or education level to comprehensively evaluate the complex trajectory of CMDs and depression. A series of sensitivity analyses had been conducted to confirm the robustness of our study.

Nevertheless, several limitations are still need to be mentioned. First, the information on SES was mainly from self-reported questionnaires at baseline, which may be subject to measurement errors. Besides, we could not capture the long term SES trajectories during follow-up. Future studies with repeated measurements are warranted to conduct to confirm these results. Second, only family income level, employment status, and education level were used to generate an overall SES parameter, which may not completely reflect different domains of SES. However, we conducted a separate analysis with utilization of TDI to represent area level of SES, and the results were almost consistent. Third, some participants were newly diagnosed with CMDs and depression simultaneously in one admission, causing the same diagnosis date for both health outcomes. We tried several different intervals (0.5 year, 1 year, 3 years and 5 years), and dropped the same-day participants. None of these additional analyses altered the results significantly. Fourth, diagnosis of depression in the main analysis mainly relied on linked inpatient medical records, which may not capture all participants with clinically significant psychopathology, as most depression is diagnosed and managed in primary care settings. This approach likely underestimates the true incidence of depression, particularly milder cases that do not require hospitalization (Glanville et al., 2021). However, this issue is relatively mitigated in our study by a supplement use of PHQ-9 questionnaires to measure depressive symptoms. Fifth, we examined only the CMD to depression pathway, not the reverse direction. The

complex interplay between CMDs and depression likely involves reciprocal causation that our study cannot fully capture. Future research should examine the depression to CMD pathway using appropriate study designs. Sixth, The UK Biobank has been shown to be less ethnically diverse and healthier than the general UK population. This may limit the generalizability of findings, as the transitions observed here may differ in other populations that are less healthy or of lower SES. However, the large sample size of UK Biobank allowed for adjustment for various health behaviors and risk factors that may impact disease progression. Seventh, we categorized ethnicity into "White" and "Other" groups due to the limited ethnic diversity in the UK Biobank cohort, where approximately 90 % of participants identified as White. While this binary categorization allowed for statistical power in our analyses, we acknowledge that it may mask important ethnic differences in the relationships between SES, CMDs, and depression. Future studies with more ethnically diverse populations should examine these relationships across specific ethnic groups to better understand how ethnicity may modify the impact of socioeconomic inequalities on disease transitions. Eighth, while we included smoking and alcohol consumption status as covariates in our analyses, we did not have comprehensive data on substance abuse, including illicit drug use, which is relatively common in the UK population. The absence of this information represents a potential source of unmeasured confounding that could influence our findings. Future research should incorporate comprehensive substance use assessments to better understand these complex relationships. Finally, it's difficult to make causality conclusions in an observational cohort study. Although we have adjusted a significant number of relevant confounders, we cannot reject the possibility of unmeasured confounders that might bias our results.

5. Conclusion

Based on a large-scale population cohort, this study provides new evidence that socioeconomic inequalities play an important role in developing CMDs, and transitions to depression. It's of great public health significance to focus on the occurrence of depression after new onset of CMDs. These findings support the need for urgent actions and reinforced efforts to address socioeconomic inequalities in prevent post-CMDs depression, and provide valuable implications for targeted intervention. Policy makers and health professionals should prioritise socioeconomically disadvantaged groups when designing and implementing secondary prevention programs on chronic diseases.

CRedit authorship contribution statement

Han Chen: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Xuemei Wang:** Writing – review & editing, Validation, Methodology. **Zhi Cao:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization, Funding acquisition. **Chenjie Xu:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

Disclosures

None of the funder had any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript.

Availability of data and materials

The data that support the findings of this study are available from UK Biobank project site, subject to registration and application process. Further details can be found at <https://www.ukbiobank.ac.uk>.

Statement

All participants provided informed consent through electronic signature. UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Reference 11/NW/03820) as a Research Tissue Bank.

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Declaration of interest statement

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.socscimed.2025.118542>.

Data availability

Data will be made available on request.

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