

Social determinants of health and risk of dementia in people with and without type 2 diabetes – findings from two large national-scale cohorts

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ABSTRACT

Introduction: Explore association between a weighted social determinants of health (SDOH) score and incident dementia in adults with and without type 2 diabetes (T2D).

Methods: Among 10,071 UK Biobank adults with T2D and 11,780 euglycemic individuals, SDOH indicators were weighted using elastic net and categorized as favorable, medium, or unfavorable. Sex- and T2D-stratified associations with incident dementia were estimated using multivariable Cox models and validated in All of Us.

Results: Over 14 years of follow-up in UKB, 247 T2D and 149 euglycemic participants developed dementia. In T2D, higher SDOH score was significantly associated with increased risk of all-cause dementia. Comparing unfavorable vs. favorable SDOH, hazard ratios (HRs) were 2.4 (95% CI: 1.7-3.6) overall, 1.7 (1.1-2.6) in men, and 5.4 (2.0-13.9) in women (Sex-interaction p 0.009). In euglycemic, corresponding HRs were 2.4 (1.4-3.8) overall, 2.4 (1.3-4.3) in men, 2.9 (0.9-8.9) in women. Stratified by SDOH category, T2D (vs. euglycemia) was significantly associated with higher dementia risk in the unfavorable/medium SDOH group: 2.9 (1.8-4.6) in all, 1.7 (0.8-3.6) in men, and 3.1 (1.1-8.7) in women.

Conclusions: Adverse SDOH was associated with higher dementia risk, with stronger T2D-related risk among medium/unfavorable SDOH groups, especially in women with T2D.

INTRODUCTION

People with type 2 diabetes (T2D) face a significantly higher risk of dementia and other cognitive impairments, compared to individuals without T2D [1, 2]. As diabetes care improves survival, more patients will reach ages at which dementia and cognitive decline become common. This intensifies the downstream burden of cognitive disability, caregiving needs, and healthcare spending [3, 4]. Consequently, these trends position cognitive outcomes as a critical next frontier for risk stratification in aging people with T2D. This shift underscores the need to look beyond traditional clinical risk factors towards upstream social determinants of health (SDOH), which may offer scalable leverage for intervention.

Studies have primarily focused on a single indicator of SDOH, which fails to capture that adverse SDOH factors often co-occur and interact. This leads to an incomplete assessment of the cumulative social burden relevant to risk of dementia and other neurocognitive dysfunction, e.g. mild cognitive impairment (MCI) [5]. Although emerging research has used a collective approach to SDOH in relation to cognitive decline [6], important research gaps remain. First, unweighted summed scores, which most studies adopted and overlooked that components contribute to outcomes differently [7]. Second, the role of cumulated SDOH burden in shaping dementia and other cognitive outcomes among high-risk adults with T2D remains underexplored, limiting translation into SDOH-

informed, risk-stratified diabetes care among aging patients. Additionally, despite women's higher susceptibility to adverse SDOH and cognitive consequences [8], the sex-specific patterns of SDOH-cognition association in people with or without diabetes have not been adequately examined [9]. Addressing these gaps is essential to inform sex-sensitive screening, risk stratification, and psychosocial support strategies aimed at improving disease management and potentially reducing dementia risk in aging adults with T2D.

In this study, we examined the association between a multidomain weighted SDOH score and incident dementia and other cognitive outcomes among individuals with and without T2D in two national cohorts. We hypothesized that a higher SDOH burden would be independently associated with a greater risk of dementia, MCI, unfavorable brain functional and cognitive outcomes, with stronger associations among individuals with T2D. We further hypothesized that women with T2D would be particularly vulnerable to dementia risk associated with unfavorable SDOH.

RESULTS

Study characteristics

A total of 10071 dementia and MCI free UKB participants with T2D were included in baseline (Supplementary Table 1). Among 6791 men, those in the unfavorable SDOH group were slightly older, had longer years of T2D, and shorter follow-up than those in the favorable or medium SDOH groups. They were also more likely to be non-White, current smokers, have higher BMI, be depressed, and have poorer performance across cognitive tests, with the exception of the Trail Making Test A (Supplementary Table 4). These patterns were also observed among women, with those in the unfavorable SDOH group having shorter follow-up and a higher prevalence of non-White race, current smokers, elevated BMI, depression, lower complex processing speed, and worse verbal declarative memory compared with those in the favorable or medium groups. These patterns were also broadly consistent in the euglycemic group for both men and women across SDOH categories.

In AoU, the T2D cohort characteristics were generally consistent with UKB. The unfavorable SDOH group was more likely to be non-white, a current smoker, and depressed for both men and women (Supplementary Table 2). For participants with unfavorable SDOH in euglycemic group, racial composition, smoking and were slightly differ between men and women (Supplementary Table 3).

The association between SDOH and risk of dementia and MCI

For all T2D participants at UKB, compared with the favorable SDOH group (dementia case/population: 46/3173), the hazard ratios (HR) for dementia were 1.36 (95%CI: 0.91-2.04) for the medium SDOH (dementia case/population: 77/3064) and 2.43 (95%CI: 1.67-3.52) for the unfavorable SDOH (dementia case/population: 124/3224), compared with the favorable ($P_{trend} < .001$). Per 1-point increment in SDOH weighted score was significantly associated with higher risk of dementia (HR: 1.47, 95%CI: 1.25-1.73) (Figure 1). A similar pattern was observed for MCI 1.27 (95% CI: 0.82-1.96) in the medium SDOH (MCI case/population: 60/3084) and 1.29 (95%CI: 0.83-1.99) in the unfavorable SDOH (MCI case/population: 63/3240) (Supplementary Figure 3).

After stratification by sex, the association between higher SDOH burden and dementia risk remained evident in both men and women with T2D. Among men, the HR for dementia were 1.16 (95%CI: 0.73-1.85) for the medium SDOH (dementia case/population: 47/2108) and 1.70 (95%CI: 1.11-2.61) for the unfavorable SDOH (dementia case/population: 80/2282), compared with the favorable ($P_{trend} = 0.009$). The corresponding associations were stronger among women, with HR of 3.19 (95%CI: 1.20-8.47) for the medium SDOH (dementia case/population: 32/1016) and 5.35 (95%CI: 2.05-13.95) for the unfavorable SDOH (dementia case/population: 44/1030) ($P_{trend} < .001$). And per 1-point increment in weighted SDOH score was also significantly associated with a higher risk of dementia for both men (HR: 1.33, 95%CI: 1.11-1.59) and women (HR: 2.19, 95%CI: 1.44-3.33) with T2D. Among adults with T2D, the association between weighted SDOH score and dementia risk differed by sex ($P_{interaction} = 0.009$). In the euglycemic group, medium (dementia case/population: 45/4000) and unfavorable SDOH (dementia case/population: 78/3759) were likewise associated with an increased dementia risk overall (HR: 1.84 and 2.28, 95%CI: 1.07-3.16 and 1.35-3.84, respectively), although in sex-stratified analyses the association persisted only among unfavorable men (dementia case/population: 59/2525) (HR: 2.40, 95%CI: 1.34-4.31). In addition, each 1-point increment in the weighted SDOH score was associated with a higher risk of dementia in the overall euglycemic group (HR: 1.43, 95%CI: 1.18-1.73) and in euglycemic men (HR: 1.42, 95%CI: 1.14-1.76).

In AoU, relative to the favorable SDOH group, T2D participants in the medium SDOH group had elevated risks of dementia (case/population: 43/4433) (HR: 2.65, 95%CI: 1.44-4.88) and MCI (case/population: 182/4433)

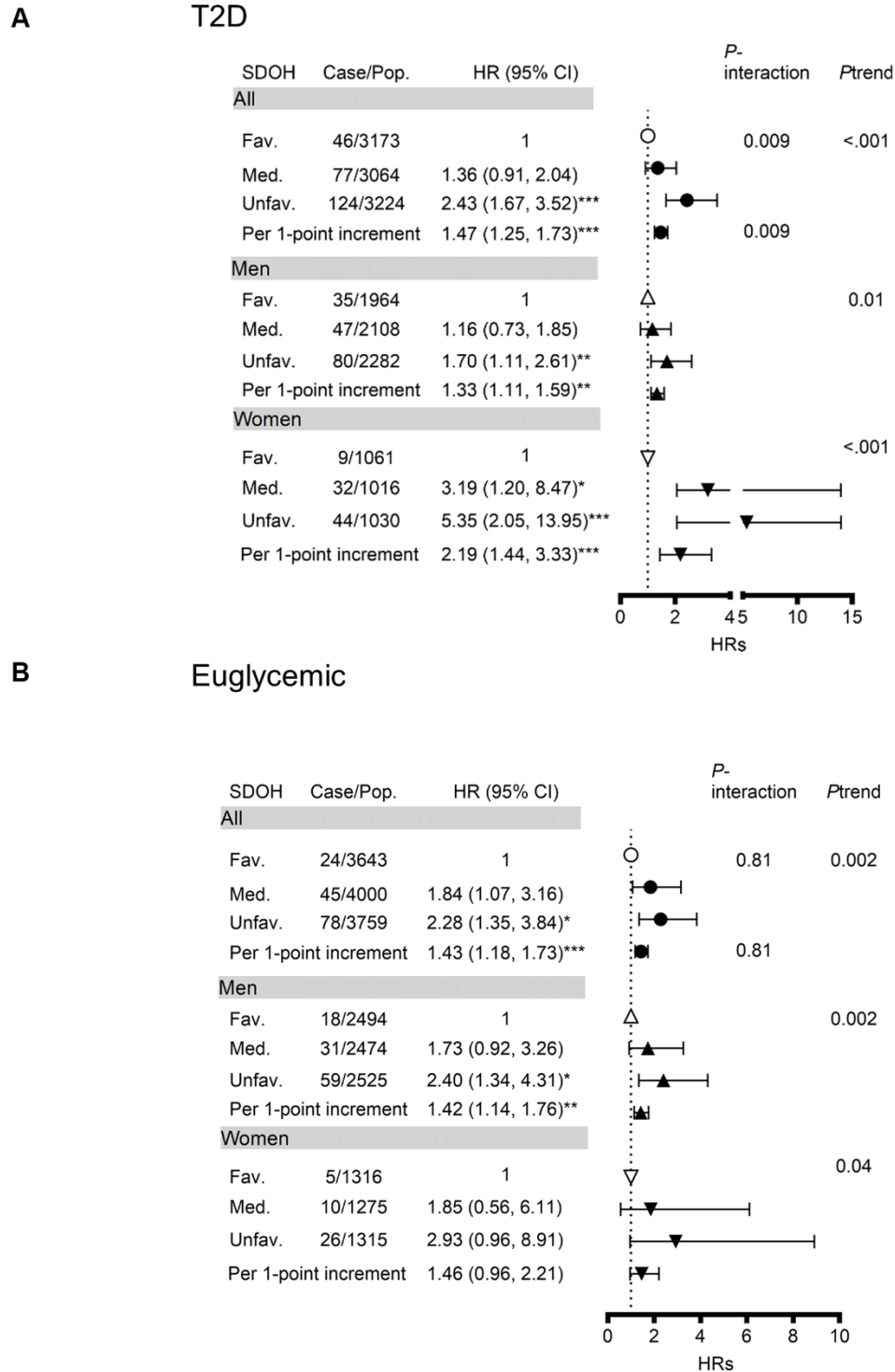


Figure 1. Adjusted hazard ratio of SDOH levels and risk of dementia in selected UKB participants and stratified by sex, (A) T2D, (B) Euglycemic. Notes: SDOH: social determinants of health, Pop.: population, T2D: type 2 diabetes, Fav.: favorable, Med.: medium, Unfav.: unfavorable, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer's disease polygenic risk score. For T2D participants, Cox model adjusted covariables including age, race, sex (all T2D or euglycemic only), smoking status, alcohol consumption, physically active, total cholesterol, years on T2D (T2D only), diabetes medications (T2D only), body mass index, hemoglobin A1C level, depression, and AD PRS, *P*-interaction was used categorical SDOH and continuous SDOH (per 1-point increment), *P*trend was calculated based on categorical SDOH (all) and dementia outcome, *: <0.05, **: < 0.01, ***: < 0.001.

(HR: 1.35, 95%CI: 1.07-1.70). The magnitude of association was greater in the unfavorable SDOH group, with HRs of 5.79 (95% CI: 3.21-10.43) for dementia (case/population: 76/4434) and 1.53 (95%CI: 1.20-1.95) for MCI (case/population: 170/4434). In sex-stratified analyses, medium and unfavorable SDOH were similarly associated with higher risks of dementia and MCI in both men and women with T2D. Comparable patterns were also observed in the euglycemic group across SDOH categories (Supplementary Figures 4, 5).

The association between T2D and risk of dementia across SDOH categories

For UKB participants, the elevated risk of dementia comparing T2D with euglycemic individuals on unfavorable/medium SDOH strata (dementia case/population: 100/3027) (HR: 2.89, 95%CI: 1.81-4.64), meanwhile, women with T2D (dementia case/population: 36/1062) had 3.1-fold higher risk of dementia (95%CI: 1.11-8.73) compared with euglycemic

women in the unfavorable/medium SDOH group (Figure 2). Similar patterns of increased risk of dementia and MCI among participants with T2D versus euglycemic individuals were also observed in AoU in unfavorable/medium SDOH strata (Supplementary Figure 6).

The association between SDOH and neuroimaging measures and cognitive scores

After adjustment for all covariates, weighted SDOH score was not significantly associated with neuroimaging or cognitive outcomes in the overall UKB T2D group (Supplementary Table 5). In sex-stratified analyses, however, each 1-point increase in weighted SDOH score was associated in men with T2D with higher total brain volume, longer Trail Making Test B completion time, and worse complex processing speed, verbal declarative memory, and non-verbal reasoning. Comparable patterns were also observed in the euglycemic group (Supplementary Table 6).

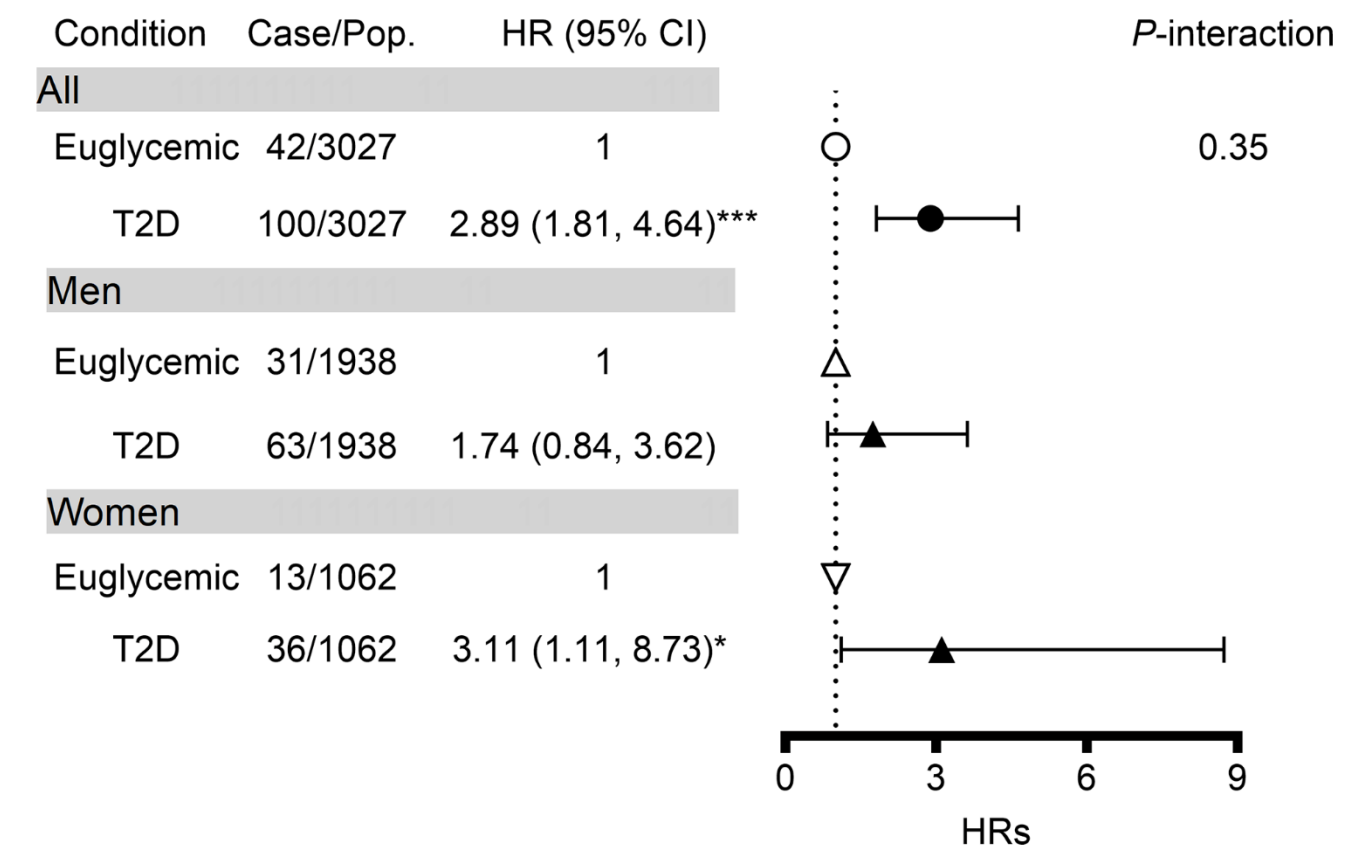


Figure 2. Adjusted relative risk of dementia between T2D and euglycemic people in UK Biobank participants in unfavorable/medium SDOH strata. Notes: SDOH: social determinants of health, Pop.: population, T2D: type 2 diabetes, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer’s disease polygenic risk score. Cox model adjusted covariables including age, race, sex, smoking status, alcohol consumption, physically active, total cholesterol, body mass index, hemoglobin A1C level, depression, and AD PRS, *P*-interaction was calculated based on categorical SDOH and dementia outcome, *: <0.05, **: < 0.01, ***: < 0.001.

Dementia subgroup analysis

In the UKB, unfavorable SDOH was associated with higher risk of vascular dementia among euglycemic participants and higher risk of unspecified dementia among participants with T2D (Supplementary Figure 7). In sex-stratified analyses, unfavorable SDOH was associated with a markedly higher risk of AD in women with T2D, but not in euglycemic women. Fine-Gray competing-risk analyses showed similar directions of association (Supplementary Tables 7, 8).

SDOH subdomains and risk of dementia and MCI

Among UKB participants with T2D, higher subdomain scores, for household income, area-level education deprivation, home ownership, loneliness, and perceived stress were associated with greater dementia risk, while household income, income quality, area-level education deprivation, home ownership, and perceived stress were associated with greater MCI risk (Figure 3 and Supplementary Figure 8). In sex-stratified analyses, household income and loneliness were associated with higher dementia risk in both men and women, with stronger associations in women, and perceived stress was additionally associated with dementia risk in women with T2D. Similar overall and sex-specific patterns were also observed in UKB participants with euglycemia and in AoU participants with and without T2D (Supplementary Figures 9–14).

DISCUSSION

We conducted a prospective cohort study in adults with and without T2D from two large national-scale datasets and found that a higher weighted SDOH score, was independently associated with higher risk dementia [10]. Among people with T2D, women have a higher risk of dementia associated with increased SDOH score compared with men. Among those with unfavorable or medium SDOH score, T2D confers a significant risk of dementia, whereas favorable SDOH appeared to offset or balance off the excess dementia risk associated with T2D.

People with higher SDOH score are likely to have fewer lifelong opportunities for education, cognitively stimulating work, and social engagement, which may reduce resilience against brain aging and lead to earlier clinical expression of vascular and structural brain injury [11]. This may be particularly impactful in T2D, because social disadvantage is associated with a higher burden of T2D and may hinder timely diagnosis and diabetes self-management [12]. As a result, people with T2D may be especially susceptible to the detrimental effects of adverse SDOH, as shown in our study that

T2D confers a 2.4-fold higher risk of dementia compared to euglycemic individuals in the unfavorable SDOH stratum. Given that T2D is already associated with cerebrovascular injury attributable to microvascular disease, endothelial dysfunction, chronic inflammation, and insulin resistance [13], adverse SDOH may intensify the negative impact in the entire diabetes-brain pathways [14]. Previous studies showed that people with T2D exhibit higher basal IL-6 and cortisol levels across the day than euglycemic individuals, reflecting an exaggerated stress-related allostatic load [15]. Such elevated basal cortisol could conjugate with interleukin-6 to promote brain structural changes relevant to dementia [16]. Although previous studies support the evidence that adverse SDOH is associated with a higher risk of dementia in people with T2D, they are limited by the single SDOH indicators or lack a standardized framework for integrating multiple SDOH components [17]. By applying a weighted multidomain SDOH score rather than relying on a single indicator or unweighted sum, our study extended prior work by capturing the cumulative and unequal contribution of co-occurring adverse SDOH to dementia risk [6, 14].

We also found that the magnitude of association between SDOH and dementia risk differed by sex in the T2D group with women with T2D showing a stronger association. These findings are consistent with prior evidence suggesting that women with T2D are more susceptible than men with T2D-related cognitive decline [18] and dementia subtypes [19]. When cognitive risk was compared within the same adverse SDOH strata, individuals in the unfavorable/medium SDOH group had higher dementia risk associated with T2D relative to matched individuals with euglycemia, suggesting that the joint burden of T2D and adverse social adversity may be detrimental to brain health. One potential explanation is that women with T2D may experience greater diabetes severity, vascular burden and psychosocial risk factors than men with T2D [20]. Prior evidence has suggested that women with T2D may experience a greater excess risk of vascular dementia than men with T2D [21]. This sex-specific vulnerability may reflect differences in diabetes-related vascular injury, including endothelial dysfunction, cerebral small vessel disease, and other pathways contributing to vascular brain injury. Women may also be more susceptible to the cognitive consequences of adverse SDOH, potentially due to differences in social, behavioral, and health care access factors. In this context, adverse SDOH may amplify diabetes-related dementia risk after diagnosis by limiting access to timely care, medication adherence, healthy food, physical activity, and diabetes self-management resources [12]. Thus, among women with T2D, the adverse cognitive impact of unfavorable SDOH may

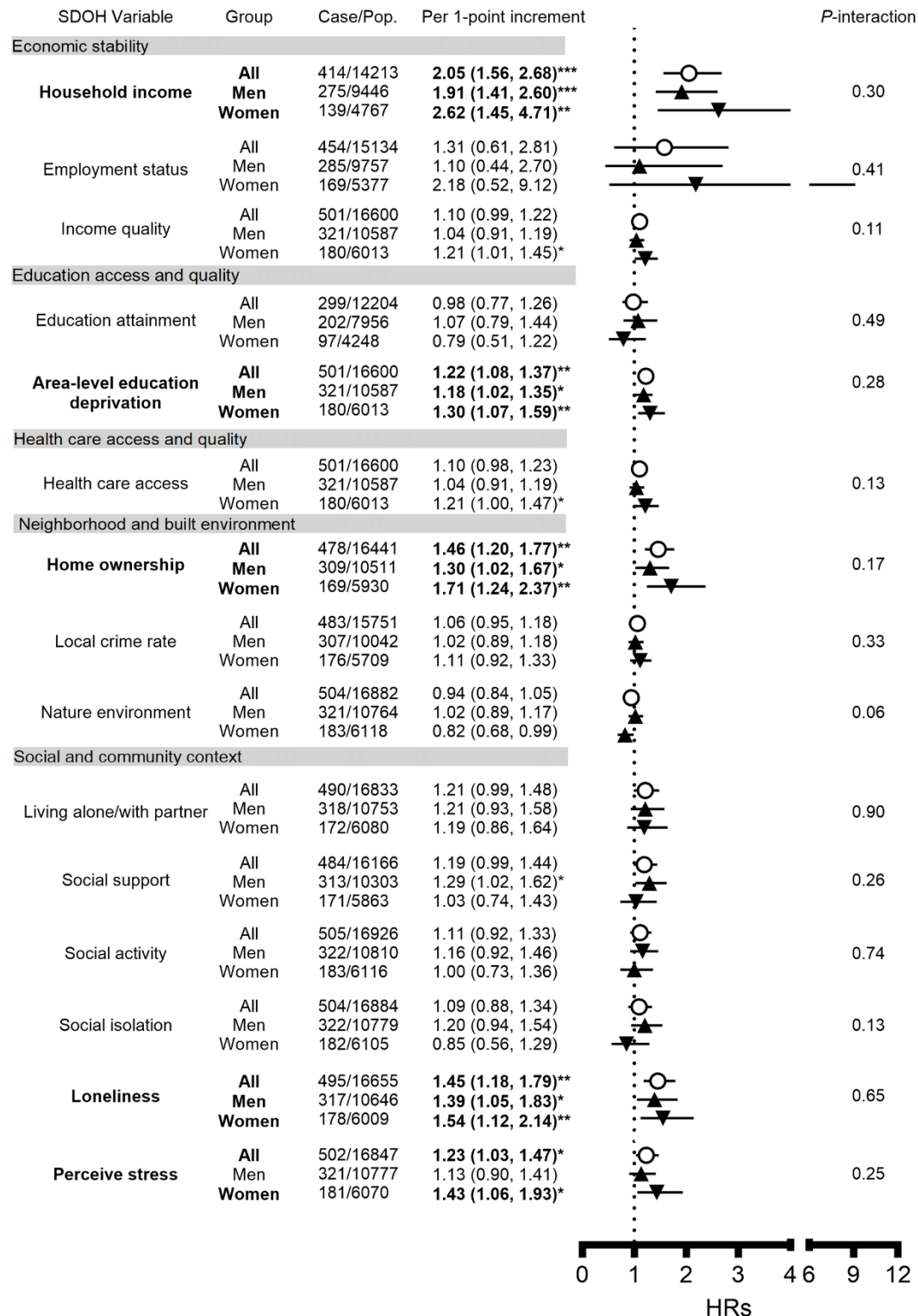


Figure 3. Adjusted hazard ratio of SDOH subdomain and risk of dementia in the UKB T2D participants and stratified by sex.
Notes: T2D: type 2 diabetes, Pop.: population, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, total cholesterol, alcohol consumption, body mass index, hemoglobin A1C level, depression, years on T2D, diabetes medication (T2D only), and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of dementia, **p* < 0.05, ** < 0.01, *** < 0.001.

accumulate over time through poorer vascular risk control, greater psychosocial stress, and sustained barriers to effective disease management [9]. Besides, the persistence of this association after adjustment for genetic risk for dementia further suggests that cumulative social disadvantage captures risk beyond inherited predisposition and may reflect modifiable exposures and constraints that shape disease trajectories in women with T2D [22]. Overall, findings from our study support the evidence that women with T2D may be especially vulnerable to the cognitive consequence of SDOH.

Our subdomain analyses suggested that household income, area-level education deprivation, and home ownership were associated with dementia in both T2D and euglycemic groups. These findings are broadly consistent with prior studies linking these adverse SDOH components to dementia risk in people with T2D [12, 23–25]. In addition, loneliness and perceived stress are significantly associated with increased risk of dementia in people with T2D but not those with euglycemia [26]. One plausible explanation is that individuals with diabetes may be more susceptible to the adverse effects of psychosocial stressors, including loneliness and perceived stress, partly due to diagnosis distress and the demanding nature of disease management. This compounds the influence of metabolic and vascular dysregulation in people with diabetes, further exacerbating their dementia risk [20]. These findings suggest that adverse socioeconomic and living conditions may shape dementia vulnerability, and that loneliness and perceived stress may reflect the psychosocial burden in people with T2D that is associated with increased dementia risk. However, none of these component-specific results should be interpreted cautiously because individual SDOH components are highly interrelated.

This study has several strengths. We leveraged two large cohorts with rich cognitive and metabolic phenotyping and genotyping information, and a sufficient number for T2D and dementia subtypes. To best of our knowledge, this is the first study that demonstrated the sex-specific association of a comprehensive SDOH measure and dementia risk and other cognitive outcomes among adults with T2D. The cross-validation across cohorts further strengthens the validity and comparability of our findings. Additionally, we conducted analysis in T2D and euglycemic group, providing comparative insights into T2D-specific patterns of cognitive risk and contributing to refined risk stratifications. Finally, we used a machine-learning based weighted SDOH score to address the limitations of unweighted summation by allowing SDOH components to contribute dementia differentially.

Our study also has limitations. First, some SDOH variables are measured differently between UKB and AoU. We addressed this limitation by mapping these cohort specific variables based on same standard [27] and harmonized them across cohorts. Another limitation of this study is the reliance on ICD diagnosis codes to identify dementia or MCI, which may lead to misclassification and the under-ascertainment of undiagnosed cases. As a result, individuals with true disease who have not yet been clinically diagnosed would not be captured in either cohort. Unfortunately, no additional clinical validation measures were available within the data source to systematically identify or confirm undiagnosed cases. This limitation may therefore lead to an underestimation of disease prevalence can could bias comparisons if the likelihood of diagnosis differs across groups. Furthermore, despite the genetic susceptibility to dementia and a wide range of confounders being controlled, residual confounding cannot be fully excluded. In addition, although two large national-scale datasets were used in the analysis, none of them is fully representative of the general population. The selection bias and healthy volunteer bias may influence both the distribution of SDOH and the ascertainment of dementia outcomes. Therefore, absolute risk estimates and prevalence patterns should not be generalized directly to the broader population. Finally, since the neuroimaging and cognitive measures were assessed cross-sectionally, whereas incident dementia was evaluated prospectively during follow-up. Consequently, the cross-sectional analyses cannot establish the temporal relationship between SDOH and neuroimaging or cognitive outcomes, which are likely to develop over time; therefore, mechanistic interpretation remains limited. In addition, the UKB imaging subset was smaller than the full analytic cohort, which may have reduced statistical power to detect modest associations, particularly after adjustment for multiple covariates. Because UKB participants were also relatively younger at the time of baseline assessment, measurable structural brain changes or cognitive impairment may not yet have been sufficiently developed in many participants. Future studies incorporating longitudinal neuroimaging, repeated cognitive assessments, inflammatory markers, proteomics, metabolomics, and other mechanistic biomarkers may help clarify pathways linking adverse SDOH burden to dementia risk.

MATERIALS AND METHODS

Study population

Data source: The primary analysis was conducted in UKB and further validated in AoU. UKB recruited over 500,000 adults between 2006 to 2010, with

extensive phenotyping and genotyping data, and long-term follow-up through linked health records. AoU designed to enroll at least one million participants from diverse backgrounds with electronic health records (EHR), survey data, biospecimens, and physical measurements [28].

Sample selection: In UKB, people with T2D defined by self-reported, diabetes medication use, hemoglobin A1C >6.5%, non-fasting glucose >200 mg/dL, or international classification of diseases (ICD) codes (Supplementary Table 14) that are available on or before the baseline assessment date [29]. We identified a group of euglycemic individuals exactly matched to T2D participants by sex, race, assessment centre, and approximate age matches, after excluding individuals with prediabetes, anti-diabetes medication use, or diabetes diagnosis codes (Supplementary Figure 1). Participants with prevalent dementia, MCI, missing SDOH components, and missing genomic data were excluded. Our complete-case analysis used censoring data updated through November 30, 2024.

In AoU, we included individuals aged 18 and above from the baseline cohort of 628,664 participants. We identified people with T2D based on at least one of the following criteria: presence of T2D diagnosis code, prescription for T2D medications (Supplementary Table 17), hemoglobin A1C >6.5%, fasting plasma glucose >125 mg/dL, or random plasma glucose level $\geq$ 200 mg/dL (Supplementary Figure 2). Individuals with any recorded type 1 diabetes diagnosis codes were excluded [30]. To identify euglycemic participants, we excluded individuals with evidence of diabetes or prediabetes based on EHR diagnosis codes, self-reported survey responses, diabetes medication use, or abnormal glycemic laboratory values [31]. These euglycemic participants exactly matched with T2D individuals by sex, race and an approximate age. Our analysis used the latest AoU Controlled Tier release (version 8) with the required phenotyping data (Supplementary Table 16), spanning May 6, 2018, to October 11, 2023.

SDOH harmonization

According to Healthy People 2030 [27] and previous works [14, 27, 32], candidate SDOH measure in each cohort were mapped to five domains including economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context. Because the two cohorts differed in questionnaire design, variable availability, and response categories, SDOH measures were harmonized at the construct level rather than as exact item-level matches. Harmonized variables were classified as comparable, approximated,

or unavailable across the two cohorts based on the degree of conceptual overlap. Each SDOH component was recorded as a binary indicator, with 0 indicating a more favorable condition and 1 indicating a more unfavorable condition. When response categories differed between cohorts, variables were collapsed using conceptually similar categories or cohort-specific distributional cutoffs. Detailed information on variable selection, definitions, and harmonization is provided in Supplementary Tables 9–11.

SDOH score

A combined weighted SDOH score was computed by elastic-net method [33] to account for the varying magnitudes of associations between SDOH variables and dementia [34] (detailed methods see Supplementary Table 18), with higher scores indicating less favorable SDOH. Participants were grouped into tertiles according to its distribution in the cohort, with the lowest (0–33.3 percentile), middle (33.3–66.7 percentile), and highest (66.7–100 percentile) tertiles representing favorable, medium, and unfavorable SDOH, respectively [14].

Genetic risk for dementia

We used standardized AD polygenic risk score (AD PRS) to quantify the genetic risk of dementia in people with T2D in UKB. For AoU, AD PRS was calculated under the current release version [35] (Supplementary Table 13).

Other covariates

Sociodemographic information was captured at baseline questionnaire, including age, sex, years on T2D, White and non-White (Black, Hispanic, more than one, Asian, Others), smoking status (non-smoker, pre-smoker 1 or years of quit $\geq$ 5, pre-smoker 2 or years of quit <5, or current smoker) [36], alcohol consumption (moderate or non-drinking, heavy drinking) [37], BMI (under/normal, overweight, obese), physically active (inactive, insufficiently active, activate) [38], hemoglobin A1C ($\geq$ or <7%), total cholesterol, anti-diabetes medications [39], depression (ICD codes, Supplementary Table 13).

Assessment of outcomes

The primary outcome of this study was dementia, AD, VD, and other dementia subtypes based on the corresponding ICD codes [40]. Our secondary outcomes (UKB only) included MCI, brain function variables, and cognitive test measures (detailed outcomes see Supplementary Table 15). Dementia and MCI diagnosis recorded on or before the baseline assessment date were

considered prevalent and excluded from incident outcome analyses. For participants from UKB, the follow-up time was calculated from the date that was one year after the baseline to the date of the outcome, death, or the censoring date (November 30, 2024), whichever occurred first. For participants from AoU, the follow-up time was calculated from the date that one year after the baseline to October 11, 2023.

Statistical analysis

Analysis of covariance and chi-square tests compared continuous and categorical variables, respectively, between participants with and without T2D across SDOH categories. We used Cox proportional hazard models to assess the associations between SDOH categories and risk of dementia and MCI, using follow-up time as the underlying time scale in T2D or non-T2D groups stratified by sex. We adjusted age, race, years of T2D (T2D group only), diabetes medications (T2D group only), smoking status, alcohol consumption, physical activity (UKB only), hemoglobin A1C level, depression, and AD PRS in the model. We accessed the proportional hazards assumption using scaled Schoenfeld residuals in the Cox model, and no evidence of violation was observed. Potential sex interactions were also tested. We then used multivariable Cox regression to examine dementia risk across SDOH categories in participants with T2D, adjusting for the same covariates. We combined those with favorable and medium SDOH as the reference group and compared them with those with unfavorable SDOH, due to small number of outcomes. For brain MRI outcomes, we used linear regression models and for cognitive performance. Besides, Fine-Gray models were used for the competing risk analysis (UKB only). The Multivariate Imputation by Chained Equations method [41] was used to handle missingness SDOH data from AoU plus cross-validation [42] (Supplementary Table 12). The sensitivity analysis for age at 65 years was conducted on both UKB and AoU cohort (Supplementary Tables 19–22, 25). We also excluded all dementia and MCI cases that were diagnosed in the first three years after initial enrollment of UKB for additional sensitivity analysis (Supplementary Tables 23, 24). Overall, data analysis was conducted on DNAnexus (for UKB) and AoU Researcher Workbench (for AoU).

Data availability

Data used in this study were obtained from UKB under application number 451358. The protocol for this study received all approvals from the UKB Review Board (www.ukbiobank.ac.uk/ethics/).

Researchers registered with UKB can apply for access to the database by completing an application, which must include a summary of the research plan, data fields required, any new data or variables that will be generated, and payment to cover the incremental costs of servicing an application (<https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>). This study also used data from the All of Us Research Program Controlled Tier dataset, version C2024Q3R8, accessed through the All of Us Researcher Workbench. The All of Us Research Program protocol, informed consent, and participant-facing materials are reviewed by the single All of Us Institutional Review Board. Access to participant-level data is available to authorized researchers affiliated with institutions that have completed a Data Use and Registration Agreement; users must complete identity verification, responsible conduct of research training, and agree to the Data User Code of Conduct before accessing the data.

Abbreviations

UKB: UK Biobank, AoU: All of Us; MCI: mild cognitive impairment; SDOH: social determinants of health; T2D: type 2 diabetes; HR: hazard ratios, CI: confidence interval; BMI: body mass index; IL-6: interleukin-6; EHR: electronic health records; ICD: international classification of diseases; PRS: polygenic risk score; AD: Alzheimer's disease; VD: vascular dementia; MRI: magnetic resonance imaging.

AUTHOR CONTRIBUTIONS

You Lu: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, writing – original draft, writing – review and editing. Yilin Yoshida: conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing – original draft, writing – review and editing.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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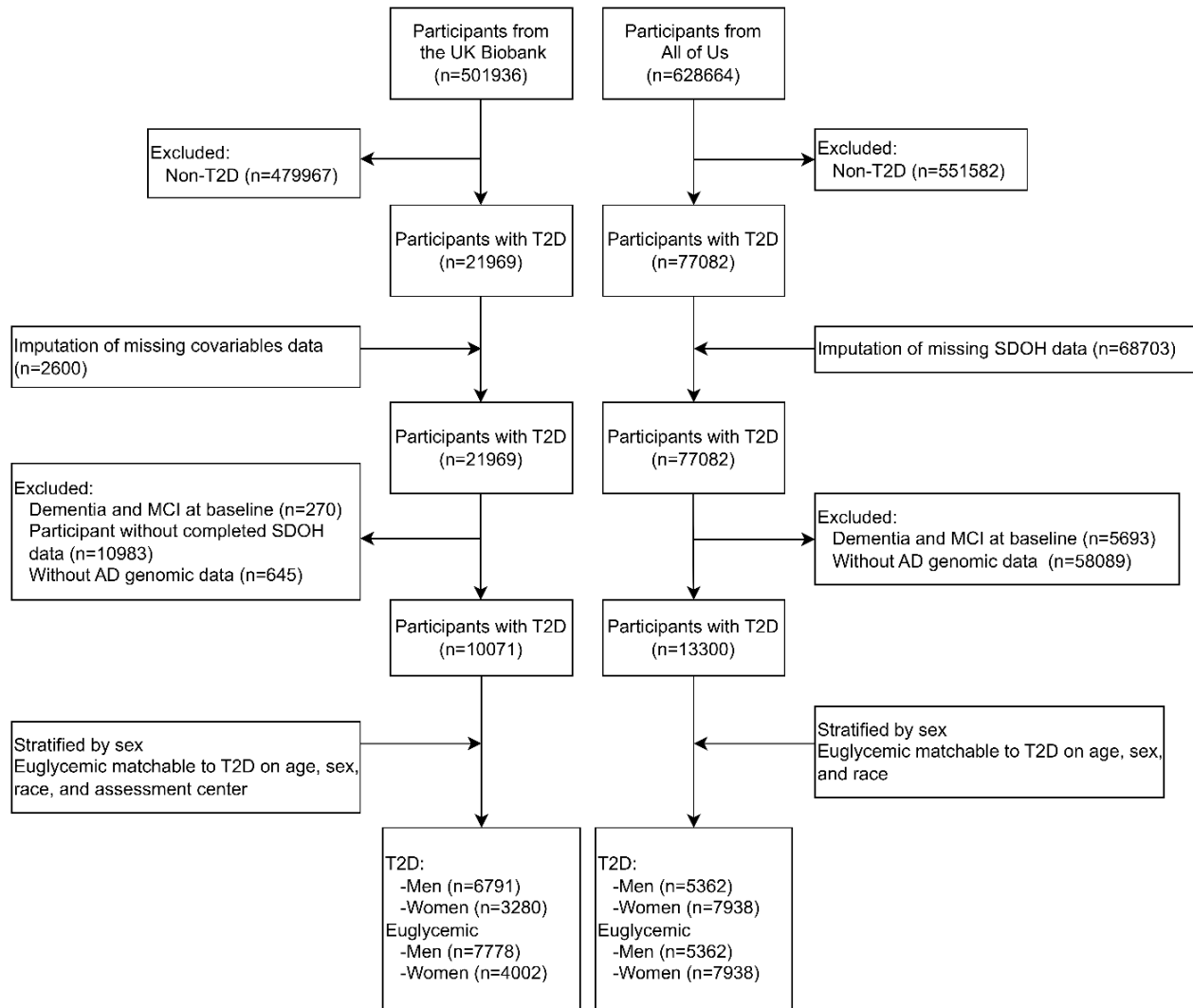
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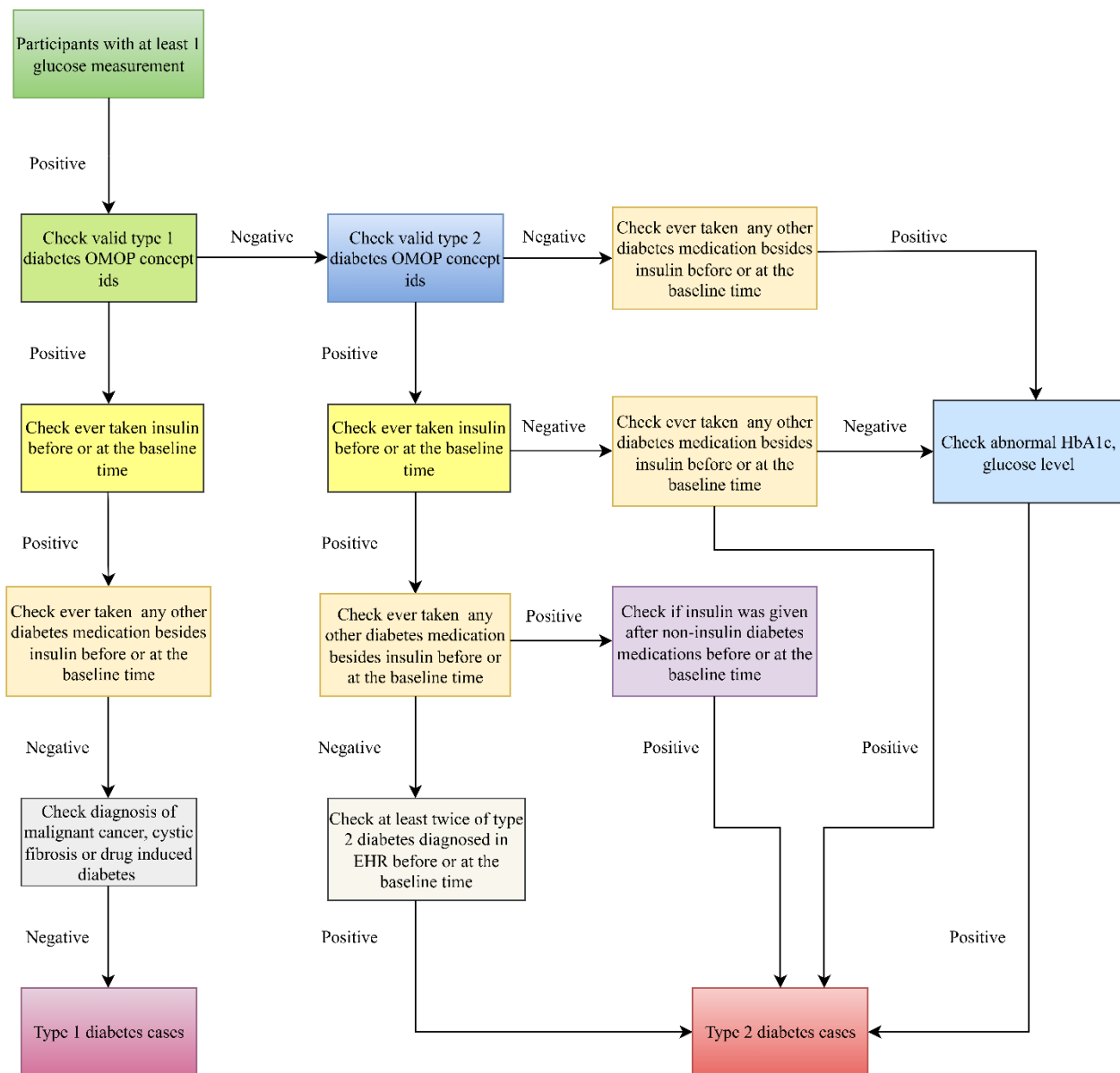
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SUPPLEMENTARY MATERIALS

Supplementary Figures



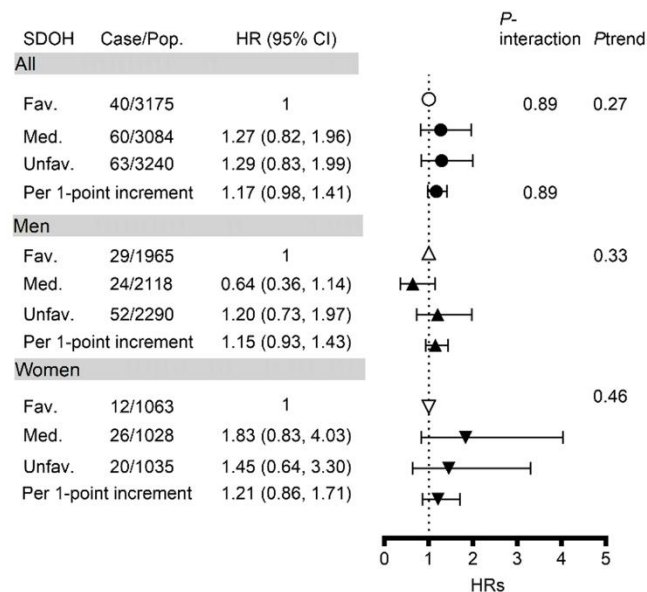
Supplementary Figure 1. Flowchart of eligible participants selection.



Supplementary Figure 2. Algorithms for identification of baseline diabetes cases from electronic health records. Notes: OMOP: Observational Medical Outcomes Partnership.

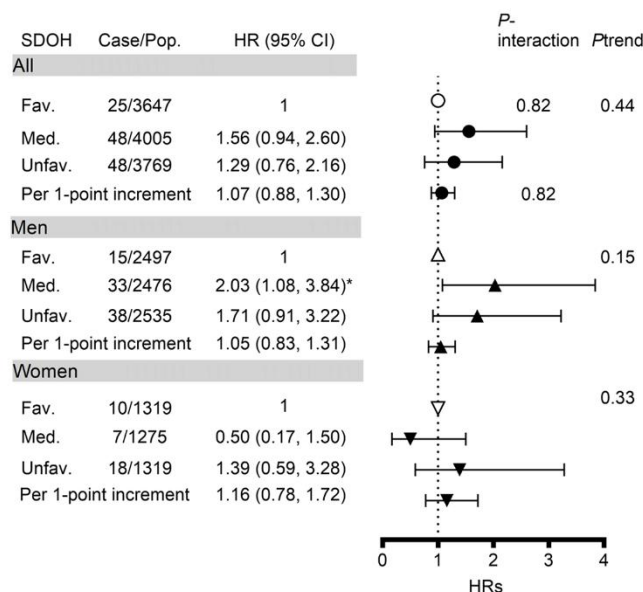
A

T2D

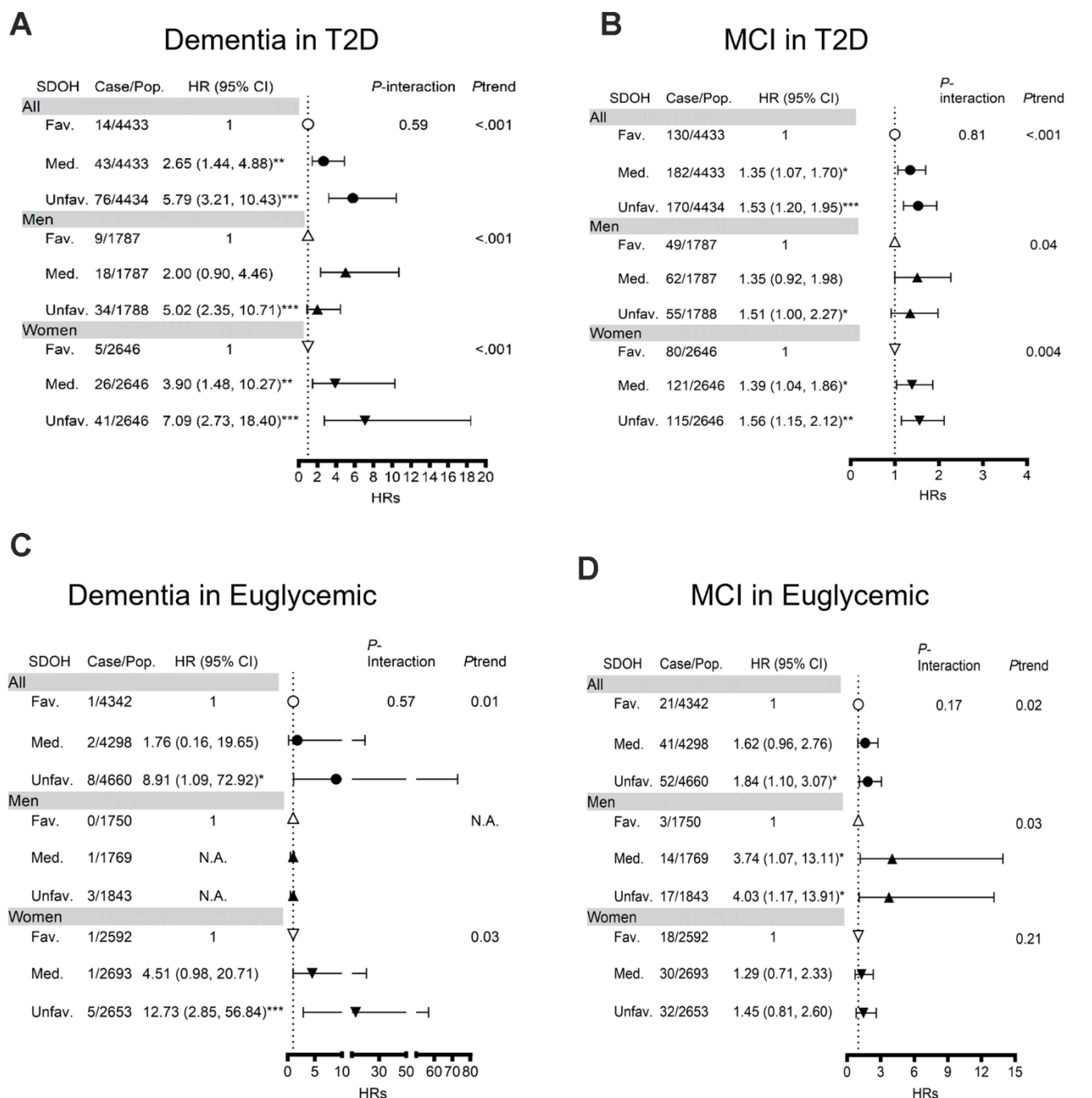


B

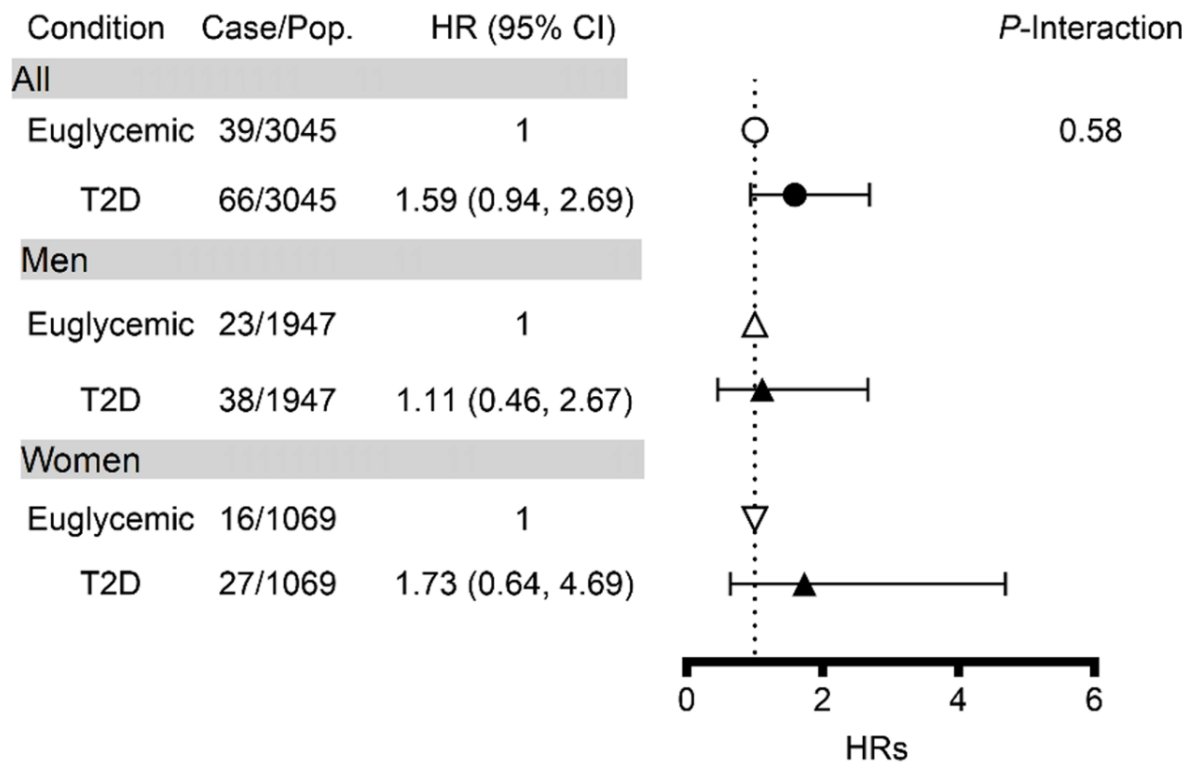
Euglycemic



Supplementary Figure 3. Adjusted hazard ratio of SDOH levels and risk of MCI in the UKB participants and stratified by sex, (A) T2D, (B) Euglycemic. Notes: MCI: mild cognitive impairment, SDOH: social determinants of health, T2D: type 2 diabetes, Fav.: favorable, Med.: medium, Unfav.: unfavorable, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer's disease polygenic risk score. Cox model adjusted covariables including age, race, sex (whole T2D or euglycemic group only), smoking status, alcohol consumption, physically active, body mass index, hemoglobin A1C level, depression, diabetes medications (T2D only), total cholesterol, and AD PRS, *P*-interaction was used categorical SDOH and continuous SDOH (per 1-point increment), *P*trend was calculated based on categorical SDOH (all) and MCI outcome, *: <0.05, **: <0.01, ***: <0.001.

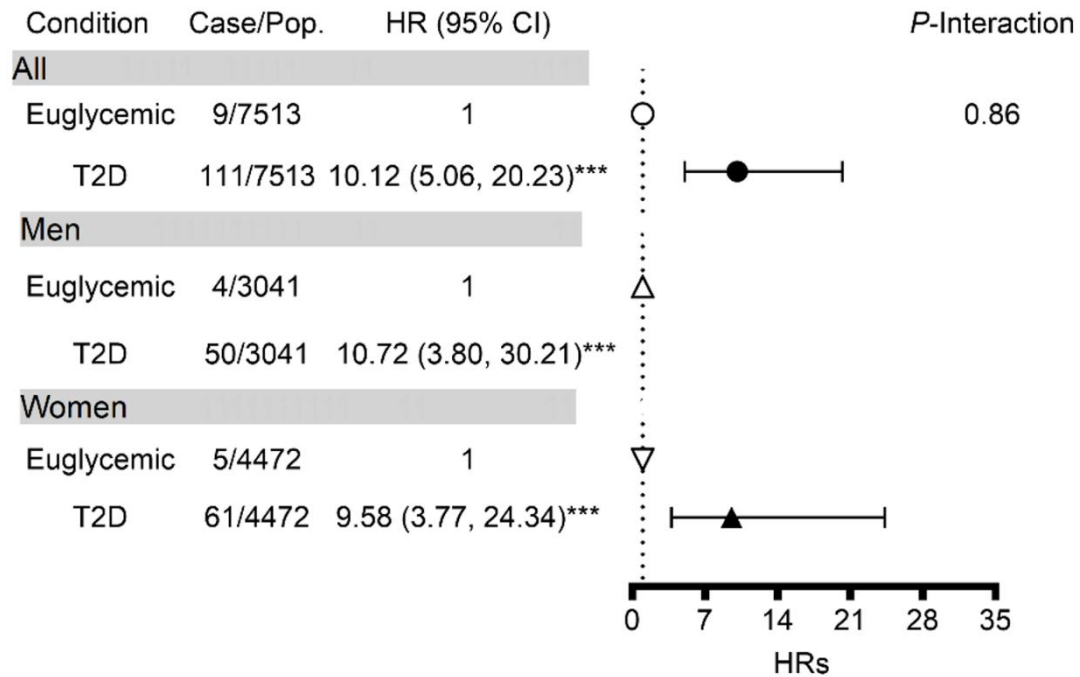


Supplementary Figure 4. Adjusted hazard ratio of SDOH levels and risk of dementia and MCI in AoU participants and stratified by sex, (A) Dementia in T2D, (B) MCI in T2D, (C) Dementia in Euglycemic, (D) MCI in Euglycemic. Notes: AoU: All of Us, SDOH: social determinants of health, Cond.: condition, Fav.: favorable, Med.: medium, Unfav.: unfavorable, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer's disease polygenic risk score, N.A.: not applicable. For euglycemic participants, Cox model adjusted covariables including age, race, sex (whole T2D group only), smoking status, alcohol consumption, body mass index, hemoglobin A1C level, depression, total cholesterol, and AD PRS. * <0.05 , ** <0.01 , *** <0.001 .

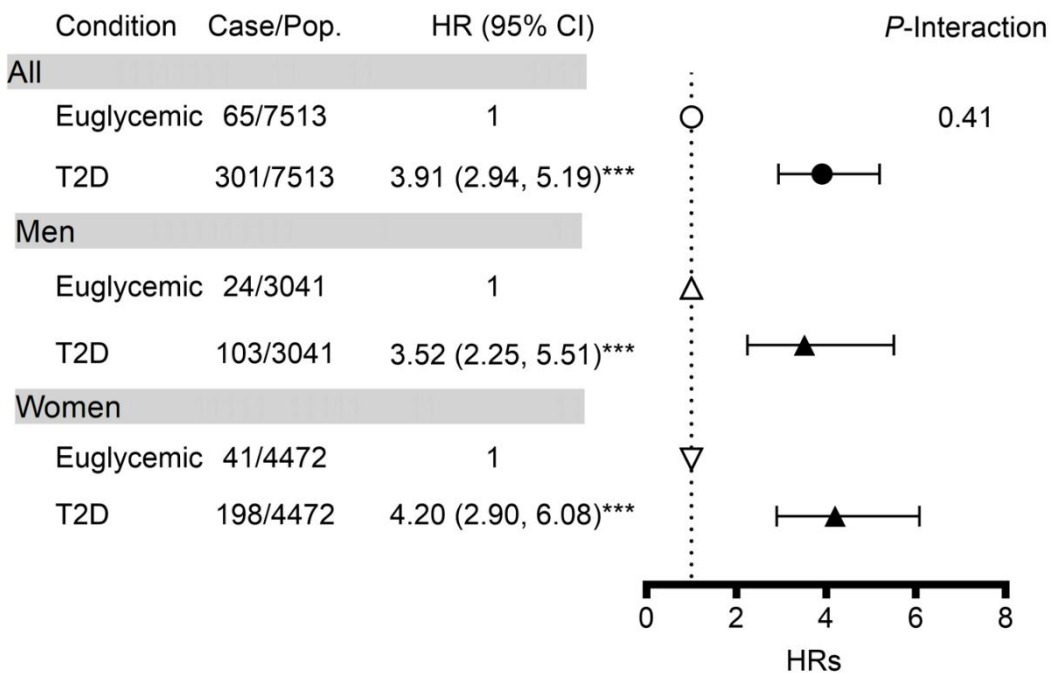


Supplementary Figure 5. Adjusted relative risk of MCI between T2D and euglycemic people in UK Biobank participants in unfavorable/medium SDOH strata. Notes: SDOH: social determinants of health, Pop.: population, MCI: mild cognitive impairment, T2D: type 2 diabetes, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer's disease polygenic risk score. Cox model adjusted covariables including age, race, sex (All only), years on T2D (T2D only), diabetes medications (T2D only), total cholesterol, smoking status, alcohol consumption, physically active, body mass index, hemoglobin A1C level, depression, and AD PRS, *P*-interaction was calculated based on categorical SDOH and MCI, dementia outcomes, *: <0.05, **: < 0.01, ***: < 0.001.

A Dementia

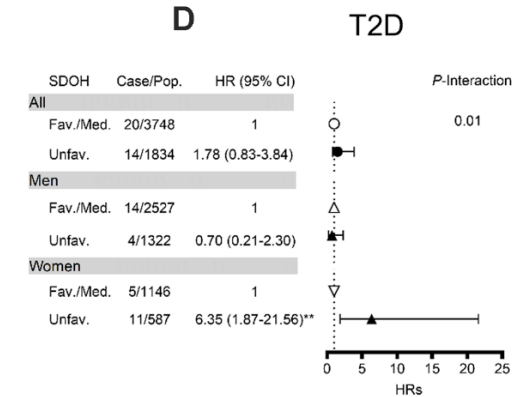
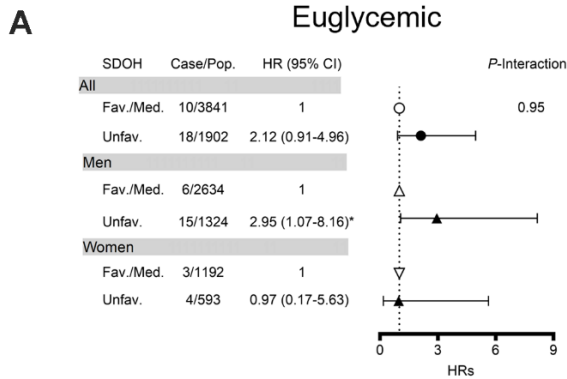


B MCI

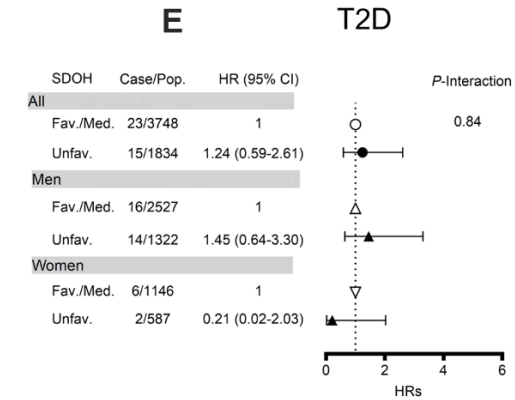
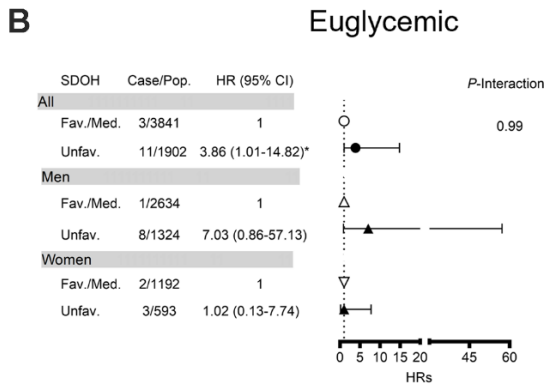


Supplementary Figure 6. Adjusted relative risk of dementia and MCI between type 2 diabetes and euglycemic people in AoU participants in unfavorable/medium SDOH strata, **(A)** Dementia, **(B)** MCI. Notes: SDOH: social determinants of health, Pop.: population, MCI: mild cognitive impairment, T2D: type 2 diabetes, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer's disease polygenic risk score. Cox model adjusted covariables including age, race, sex (All only), years on T2D (T2D only), total cholesterol, diabetes medications (T2D only), smoking status, alcohol consumption, body mass index, hemoglobin A1C level, depression, and AD PRS, *P*-interaction was calculated based on categorical SDOH and MCI, dementia outcomes, *: <0.05, **: <0.01, ***: <0.001.

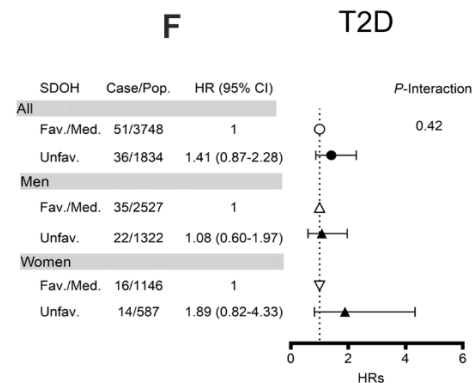
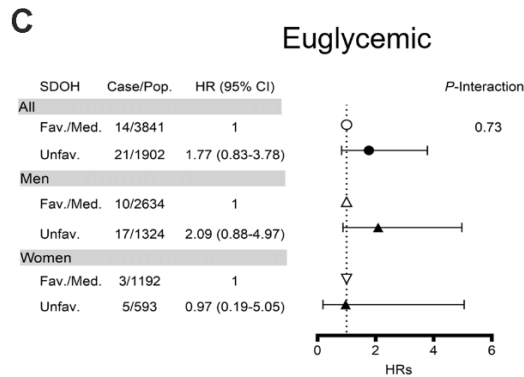
AD



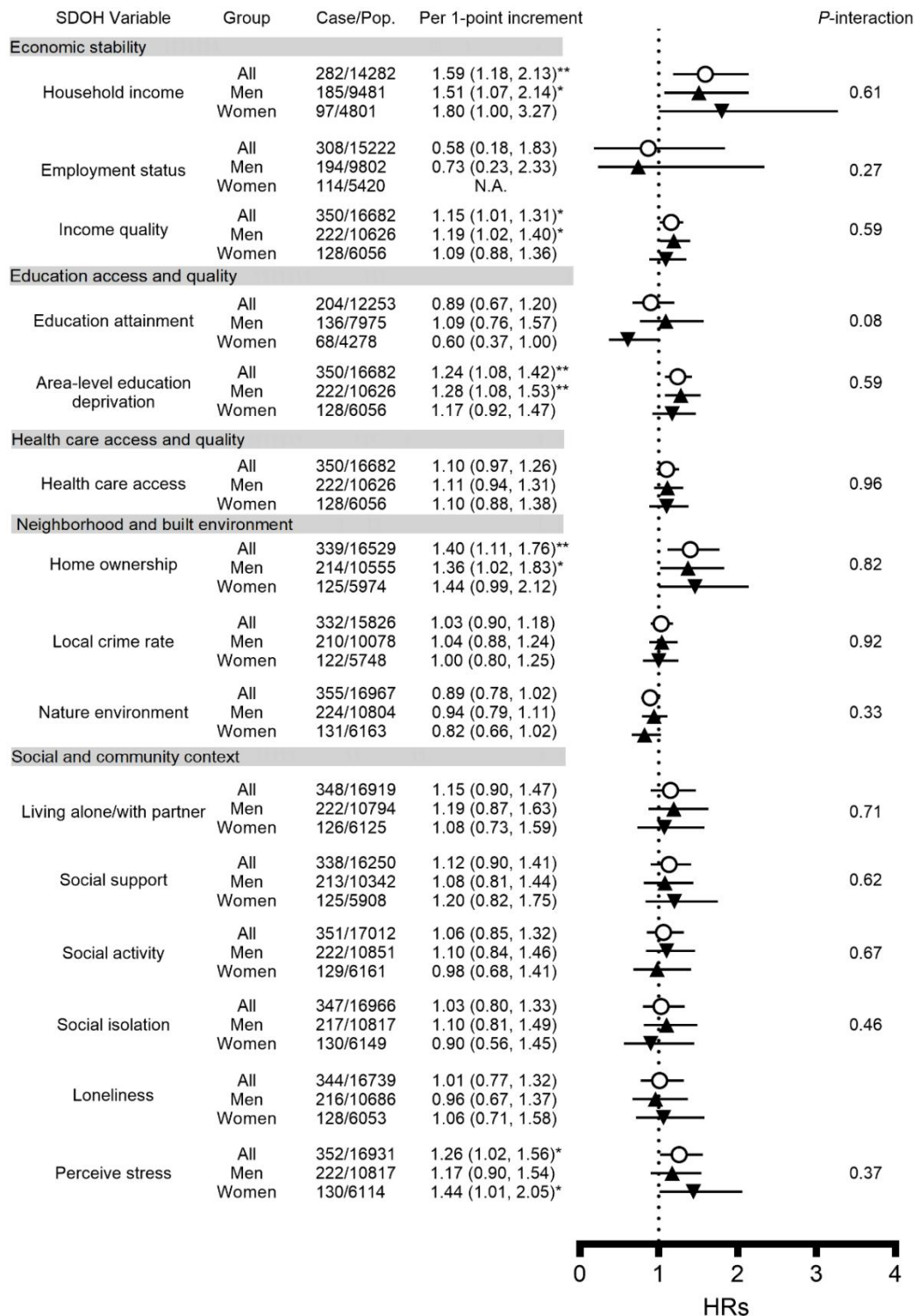
VD



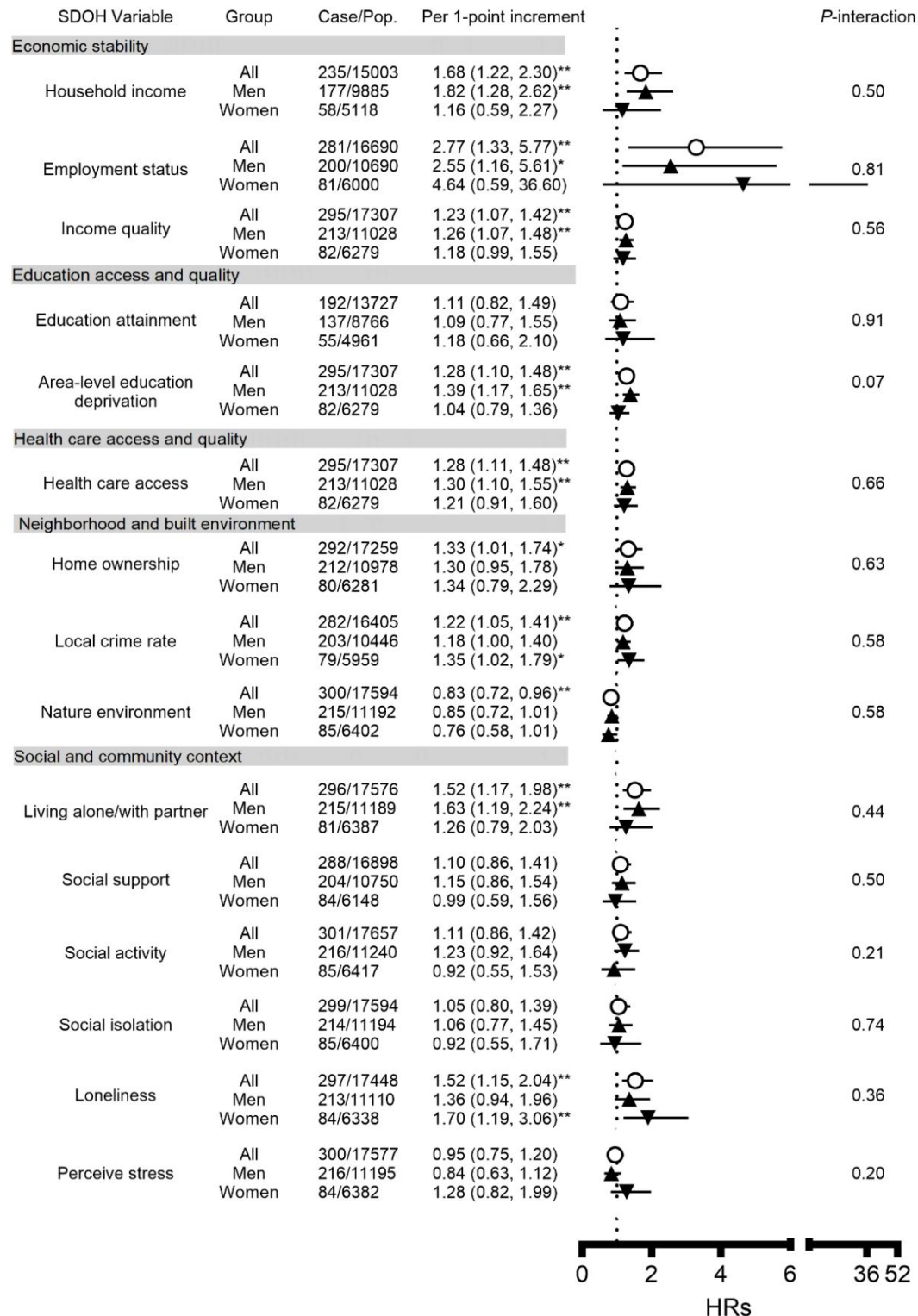
Unspecific dementia



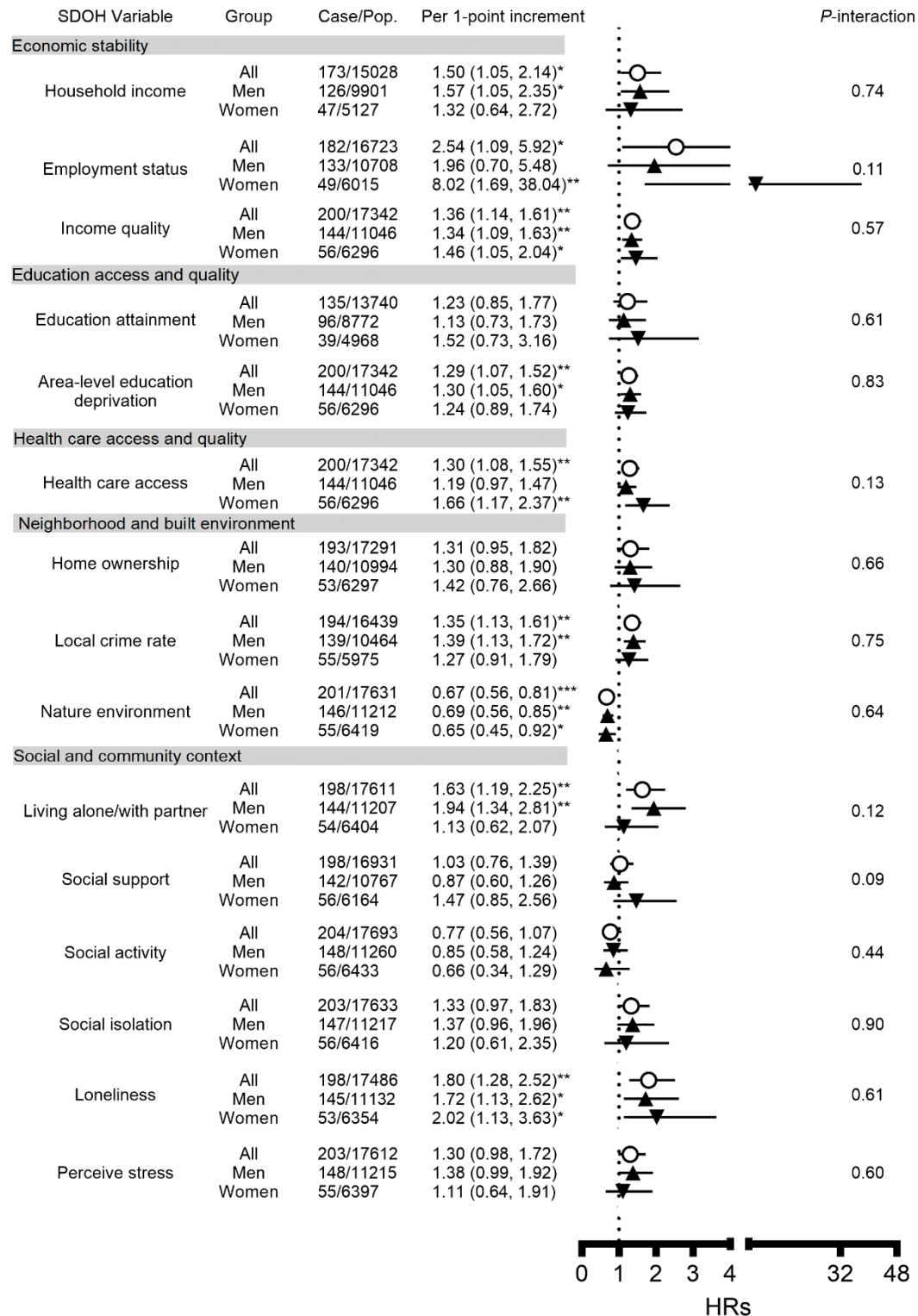
Supplementary Figure 7. Adjusted hazard ratio of SDOH levels and risk of dementia subtypes in the UKB participants and stratified by sex, (A) Euglycemic in AD, (B) Euglycemic in VD, (C) Euglycemic in unspecific dementia, (D) T2D in AD, (E) T2D in VD, (F) T2D in unspecific dementia. Notes: AD: Alzheimer's disease, VD: vascular dementia, SDOH: social determinants of health, T2D: type 2 diabetes, Fav./Med.: favorable or medium, Unfav.: unfavorable, HRs: hazard ratio, CI: confidence interval, AD PRS: Alzheimer's disease polygenic risk score. For euglycemic participants, Cox model adjusted covariables including age, race, sex (whole group only), physically active, smoking status, alcohol consumption, total cholesterol, years on T2D (T2D group only), diabetes medication (T2D group only), body mass index, hemoglobin A1C level, depression, and AD PRS. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



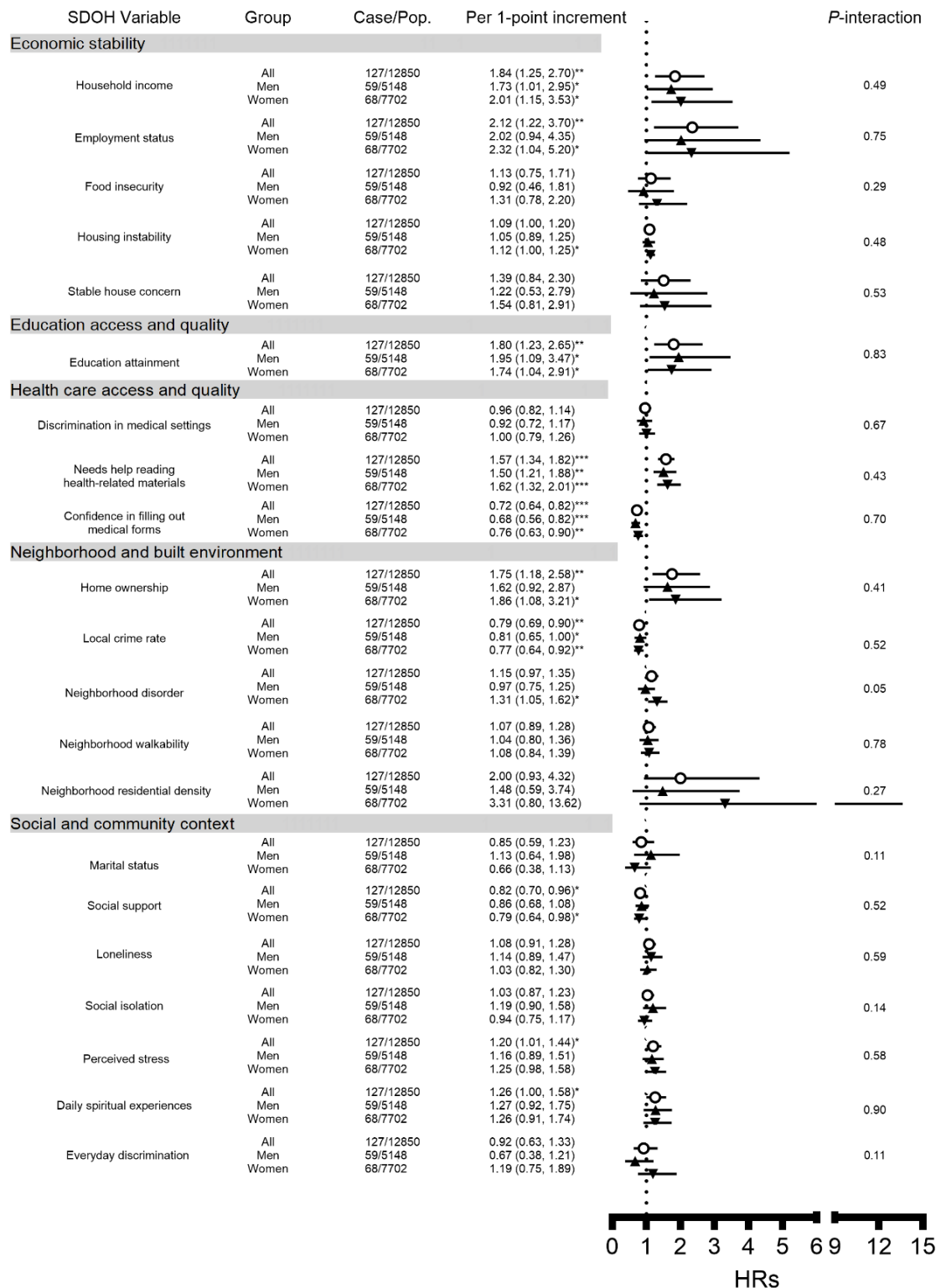
Supplementary Figure 8. Adjusted hazard ratio of SDOH subdomain and risk of MCI in the UKB T2D participants and stratified by sex. Notes: T2D: type 2 diabetes, MCI: mild cognitive impairment, Pop.: population, N.A.: not applicable, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, alcohol consumption, body mass index, hemoglobin A1C level, depression, total cholesterol, years on T2D, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of MCI, **p* < 0.05, ***p* < 0.01, ****p* < 0.001.



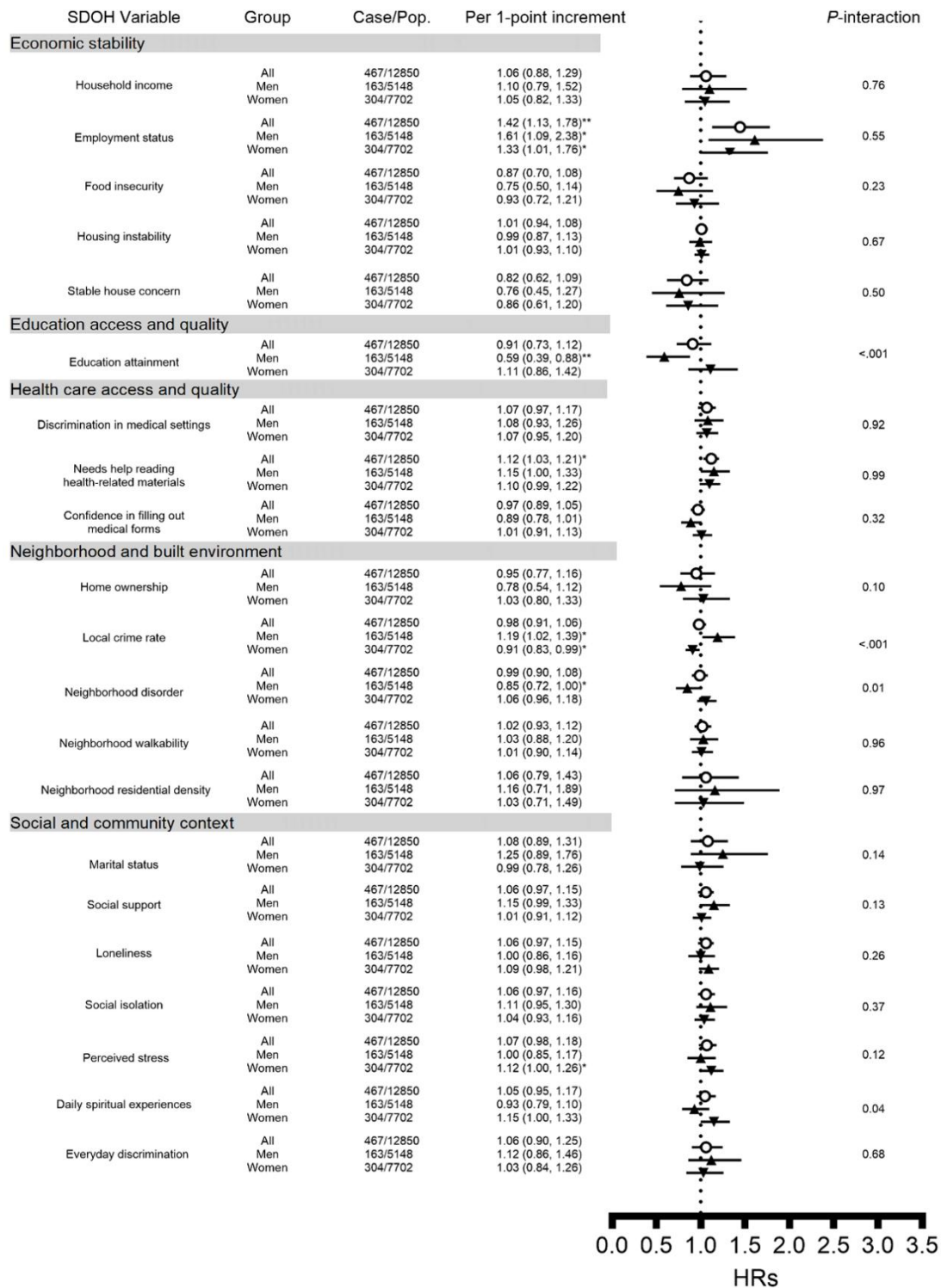
Supplementary Figure 9. Adjusted hazard ratio of SDOH subdomain and risk of dementia in the UKB euglycemic participants and stratified by sex. Notes: Pop.: population, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, alcohol consumption, body mass index, hemoglobin A1C level, total cholesterol, depression, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of dementia, **p* < 0.05, ***p* < 0.01, ****p* < 0.001.



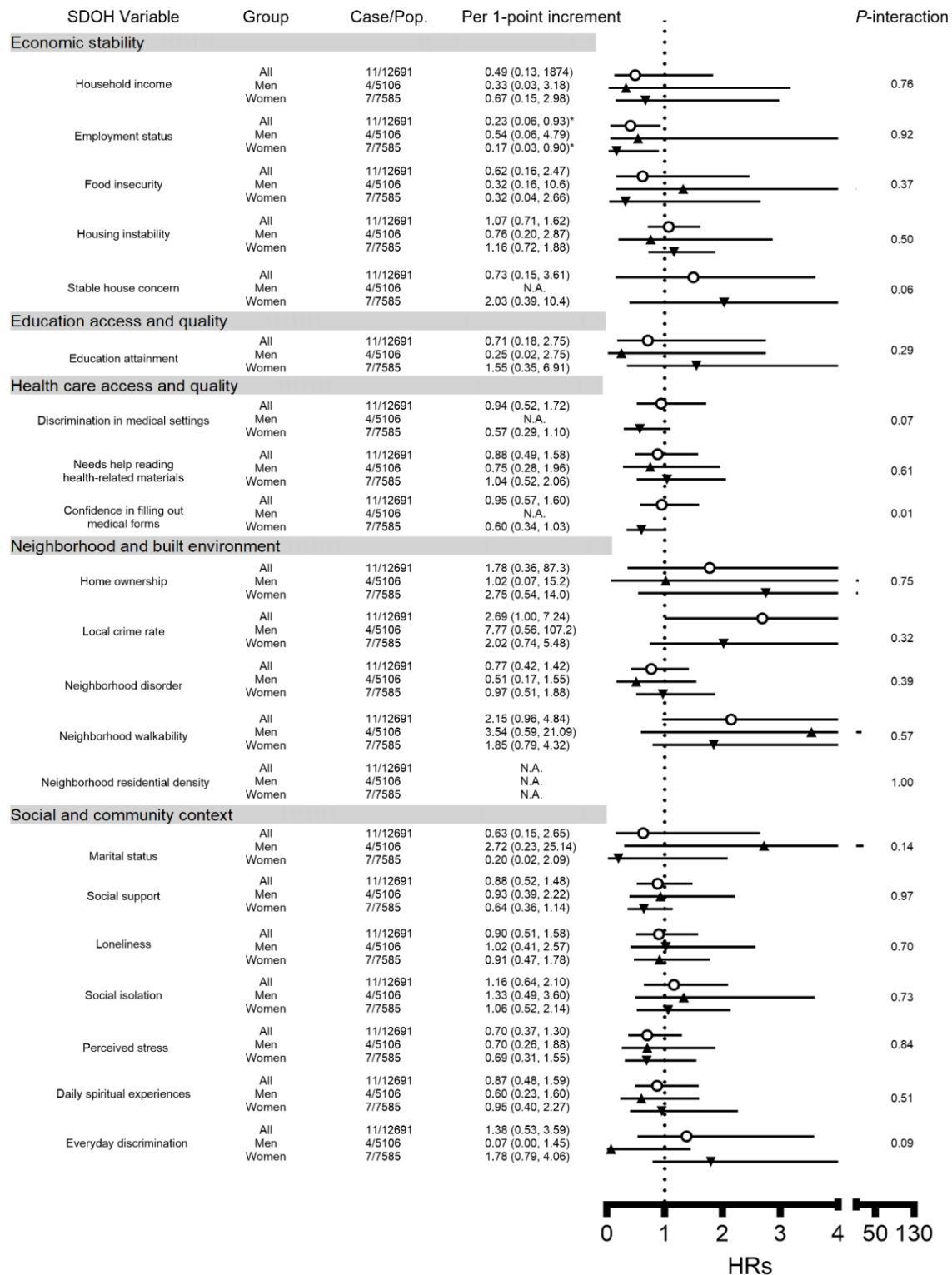
Supplementary Figure 10. Adjusted hazard ratio of SDOH subdomain and risk of MCI in the UKB euglycemic participants and stratified by sex. Notes: MCI: mild cognitive impairment, Pop.: population, N.A.: not applicable, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, alcohol consumption, total cholesterol, body mass index, hemoglobin A1C level, depression, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of MCI, **p* < 0.05, ***p* < 0.01, ****p* < 0.001.



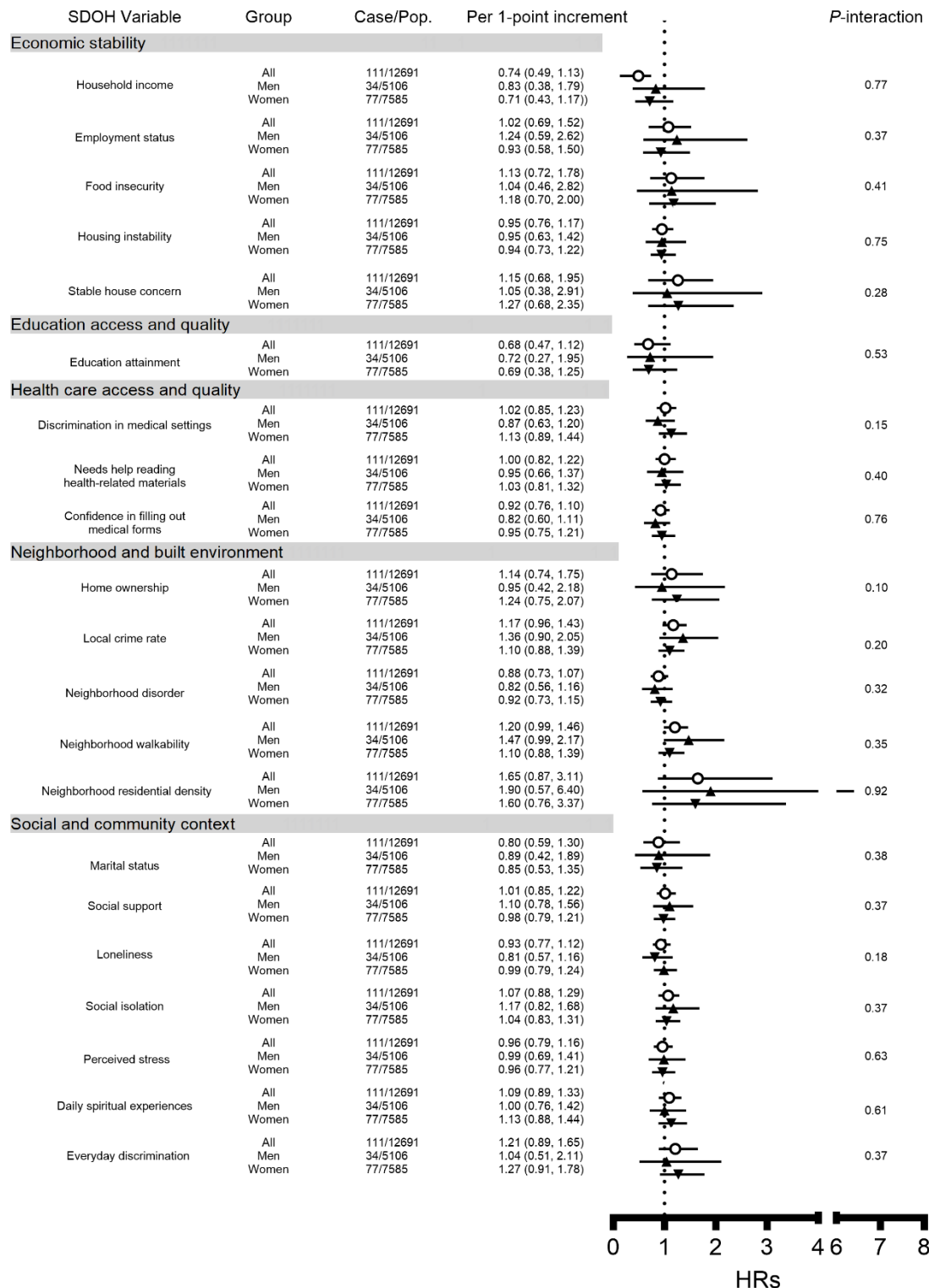
Supplementary Figure 11. Adjusted hazard ratio of SDOH subdomain and risk of dementia in the AoU T2D participants and stratified by sex. Notes: Pop.: population, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, alcohol consumption, body mass index, hemoglobin A1C level, total cholesterol, depression, years on T2D, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of dementia, * <0.05 , ** <0.01 , *** <0.001 .



Supplementary Figure 12. Adjusted hazard ratio of SDOH subdomain and risk of MCI in the AoU T2D participants and stratified by sex. Notes: T2D: type 2 diabetes, MCI: mild cognitive impairment, Pop.: population, N.A.: not applicable, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, total cholesterol, alcohol consumption, body mass index, hemoglobin A1C level, depression, years on T2D, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of MCI, **p*<0.05, ***p*<0.01, ****p*<0.001.



Supplementary Figure 13. Adjusted hazard ratio of SDOH subdomain and risk of dementia in the AoU euglycemic participants and stratified by sex. Notes: Pop.: population, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health, N.A.: not applicable. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), total cholesterol, smoking status, alcohol consumption, body mass index, hemoglobin A1C level, depression, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of dementia, **p* < 0.05, ***p* < 0.01, ****p* < 0.001.



Supplementary Figure 14. Adjusted hazard ratio of SDOH subdomain and risk of MCI in the AoU euglycemic participants and stratified by sex. Notes: MCI: mild cognitive impairment, Pop.: population, N.A.: not applicable, AD PRS: Alzheimer's disease polygenic risk score, SDOH: social determinants of health. For each SDOH sub-domain, Cox model adjusted covariables including age, race, sex (All only), smoking status, total cholesterol, alcohol consumption, body mass index, hemoglobin A1C level, depression, and AD PRS. *P*-interaction was computed as for sex as per 1-point of SDOH (treated as continuous) increment to the risk of MCI, * <0.05 , ** <0.01 , *** <0.001 .

Supplementary Tables

Please browse Full Text version to see the data of Supplementary Tables 1–4, 7, and 8.

Supplementary Table 1. Demographic characteristics of selected UK Biobank participants under different SDOH levels stratified by sex.

Notes: SDOH: social determinants of health, SD: standard deviation, AD PRS: Alzheimer's disease polygenic risk score, T2D: type 2 diabetes, BMI: body mass index, Pre-smoker: previous smoker, *: moderate or nondrinking defined as two or less than two drinks per week, heavy drinking defined as more than two drinks per week, [¶]: Inactive defined as 0 minutes of activities per week, Insufficiently active defined as less than 150 minutes of moderate activities per week or less than 75 minutes of vigorous activities per week or any equivalent combination, Active defined as more than 150 minutes of moderate activities per week or more than 75 minutes of vigorous activities per week or any equivalent combination. ^a: one-way ANOVA, ^b: Chi-sq test, ^c: Kruskal-Wallis test, pvalue for men [■]: <.05, ^{■■}: <.01, ^{■■■}: <.001, pvalue for women [○]: <.05, ^{○○}: <.01, ^{○○○}: <.001.

Supplementary Table 2. Demographic characteristics of type 2 diabetes population in AoU under different SDOH levels stratified by sex.

Notes: SDOH: social determinants of health, SD: standard deviation, AD PRS: Alzheimer's disease polygenic risk score, BMI: body mass index, N.A.: not applicable, [§]: for participants from AoU, smoking status was defined as current smoker or non-smoker, [¶]: for participants from AoU, alcohol consumption was defined as non-drinking and drinking, ^a: one-way ANOVA, ^b: Chi-sq test. For AoU, total sample size after SDOH imputed by multivariate imputation by chained equations approach.

Supplementary Table 3. Demographic characteristics of euglycemic population in AoU under different SDOH levels stratified by sex.

Notes: SDOH: social determinants of health, SD: standard deviation, AD PRS: Alzheimer's disease polygenic risk score, BMI: body mass index, N.A.: not applicable, [§]: for participants from AoU, smoking status was defined as current smoker or non-smoker, [¶]: for participants from AoU, alcohol consumption was defined as non-drinking and drinking, ^a: one-way ANOVA, ^b: Chi-sq test. For AoU, total sample size after SDOH imputed by multivariate imputation by chained equations approach.

Supplementary Table 4. Brain MRI and cognitive test measurement of selected UK Biobank participant under different SDOH levels stratified by sex.

Notes: MRI: magnetic resonance imaging, SDOH: social determinants of health, IQR: the interquartile range, *: moderate or nondrinking defined as two or less than two drinks per week, heavy drinking defined as more than two drinks per week, [¶]: Inactive defined as 0 minutes of activities per week, Insufficiently active defined as less than 150 minutes of moderate activities per week or less than 75 minutes of vigorous activities per week or any equivalent combination, Active defined as more than 150 minutes of moderate activities per week or more than 75 minutes of vigorous activities per week or any equivalent combination. ^a: one-way ANOVA, ^b: Chi-sq test, ^c: Kruskal-Wallis test, ¹: Trail making test A measures processing speed and attention (unit: deciseconds), ²: trail making test B assesses executive function (task-switching), often quantified as trail making test B minus trail making test A to isolate executive function (unit: deciseconds), ³: a total of 13 questions were asked from fluid intelligence test (data range from 0 to 13, unit: correct counts), ⁴: maximum digits remembered correctly from numeric memory test (data range from 2 to 12, unit: correct counts), ⁵: a total number of symbol digit matches made correctly from symbol-digit test within one minute (data range from 0 to 38, unit: correct counts), ⁶: a total number of word pairs correctly associated from paired associate learning (data range from 0 to 10, unit: correct counts), ⁷: a total number of puzzles correctly solved in matrix test (data range from 0 to 15, unit: correct counts).

Supplementary Table 5. Multivariable linear regression models examining the association between the weighted SDOH score (per 1-point increment) and neuroimaging measures from MRI and cognitive test scores in UKB type 2 diabetes participants by sex.

	All	Men	Women	<i>P</i> -Interaction
	β /(95% CI)	β /(95% CI)	β /(95% CI)	
MRI				
Total brain volume [§] (cm ³)	5305/ (-3505 to 14114)	5703/ (125 to 11282)*	5211/ (-4102 to 14524)	0.93
White matter volume [§] (cm ³)	2813/ (-3024 to 8650)	3587/ (-204 to 7378)	2873/ (-2917 to 8663)	0.81
Grey matter volume [§] (cm ³)	2492/ (-2932 to 7916)	2116/ (-1322 to 5554)	2338/ (-3347 to 8023)	0.9
Left hippocampal volume [§] (cm ³)	-40.3/ (-120.7 to 40.1)	20.4/ (-28.2 to 69.1)	-64.9/ (-156.1 to 26.3)	0.29
Right hippocampal volume [§] (cm ³)	-37.4/ (-121.7 to 46.8)	36.5/ (-16.3 to 89.4)	-63.7/ (-152.4 to 24.9)	0.2
White matter hyperintensity volume [§] (cm ³)	315/ (-1339 to 1970)	-65/ (-1053 to 1184)	172/ (-1298 to 1642)	0.81
Cognitive test				
Trail making test A ^{a,¶} (deciseconds)	-0.3%/ (-4.6% to 4.3%)	0.2%/ (-2.6% to 3.0%)	-0.5%/ (-4.8% to 4.0%)	0.77
Trail making test B ^{b,¶} (deciseconds)	0.6%/ (-4.8% to 6.3%)	6.6%/ (3.0% to 10.3%)**	1.0%/ (-5.1% to 7.5%)	0.08
Verbal/numerical reasoning [†] (correct counts ^c)	-2.0%/ (-6.7% to 2.9%)	-2.9%/ (-6.0% to 0.3%)	-1.8%/ (-6.7% to 3.3%)	0.69
Working memory [†] (correct counts ^d)	-1.3%/ (-7.6% to 5.4%)	-3.0%/ (-6.9% to 1.0%)	-0.7%/ (-7.4% to 6.4%)	0.63
Complex processing speed [†] (correct counts ^e)	-2.9%/ (-6.3% to 0.7%)	-4.3%/ (-6.5% to -2.1%)**	-2.4%/ (-6.0% to 1.4%)	0.49
Verbal declarative memory [†] (correct counts ^f)	-4.8%/ (-10.0% to 0.7%)	-6.0%/ (-9.5% to -2.4%)*	-4.8%/ (-10.1% to 0.8%)	0.67
Non-verbal reasoning [†] (correct counts ^g)	-0.6%/ (-5.3% to 4.4%)	-4.6%/ (-7.6% to -1.6%)*	-0.3%/ (-5.3% to 4.9%)	0.16

Notes: MRI: magnetic resonance imaging, SDOH: social determinants of health, T2D: type 2 diabetes, MRI: magnetic resonance imaging, C.I.: confidence interval, SD: standard deviation, [§]: linear regression model used to compute the β , [¶]: generalized linear model with gamma distribution and log link used to compute the β , [†]: Negative binomial regression with log link used to compute the β , ^a: trail making test A (TMT-A) measures processing speed and attention. ^b: trail making test B (TMT-B) assesses executive function (task-switching), often quantified as TMT-B minus TMT-A to isolate executive function. ^c: a total of 13 questions were asked from fluid intelligence test (data range from 0 to 13), ^d: maximum digits remembered correctly from numeric memory test (data range from 2 to 12), ^e: a total number of symbol digit matches made correctly from symbol-digit test within one minute (data range from 0 to 38), ^f: a total number of word pairs correctly associated from paired associate learning (data range from 0 to 10), ^g: a total number of puzzles correctly solved in matrix test (data range from 0 to 15). Model adjusted for age, sex (in the overall T2D group only), race, smoking status, alcohol consumption, physically active, years on T2D, diabetes medications, total cholesterol, body mass index, hemoglobin A1C level, depression, and Alzheimer's disease polygenic risk score, * <0.05, ** <.001.

Supplementary Table 6. Multivariable linear regression models examining the association between the weighted SDOH score (per 1-point increment) and neuroimaging measures from MRI and cognitive test scores in UKB euglycemic participants by sex.

	All β /(95% CI)	Men β /(95% CI)	Women β /(95% CI)	<i>P</i> -Interaction
MRI				
Total brain volume [§] (cm ³)	2821/ (-3206 to 8849)	-382/ (-4312 to 3548)	2684/ (-3331 to 8699)	0.4
White matter volume [§] (cm ³)	1363/ (-2559 to 5285)	-1181/ (-3724 to 1362)	1367/ (-2611 to 5345)	0.28
Grey matter volume [§] (cm ³)	1458/ (-2215 to 5131)	799/ (-1623 to 3221)	1317/ (-2233 to 4868)	0.81
Left hippocampal volume [§] (cm ³)	48.6/ (-9.0 to 106.3)	36.4/ (-1.4 to 74.1)	47.1/ (-9.7 to 103.9)	0.68
Right hippocampal volume [§] (cm ³)	72.7/ (15.1 to 130.2)*	20.3/ (-17.8 to 58.3)	60.6/ (5.6 to 115.6)*	0.1
White matter hyperintensity volume [§] (cm ³)	-89/ (-917 to 739)	320 (-224 to 865)	-151/ (-999 to 697)	0.44
Cognitive test				
Trail making test A ^{a,¶} (deciseconds)	-0.1%/ (-3.1% to 3.2%)	1.5%/ (-0.5% to 3.5%)	0.6%/ (-2.7% to 3.9%)	0.37
Trail making test B ^{b,¶} (deciseconds)	1.2%/ (-2.5% to 5.1%)	4.8%/ (2.2% to 7.3%)**	2.2%/ (-1.6% to 6.2%)	0.16
Verbal/numerical reasoning [†] (correct counts ^c)	-2.0%/ (-5.4% to 1.5%)	-3.4%/ (-5.6% to -1.2%)*	-2.2%/ (-5.7% to 1.4%)	0.52
Working memory [†] (correct counts ^d)	1.0%/ (-3.5% to 5.6%)	-2.7%/ (-5.5% to 0.1%)	1.2%/ (-3.4% to 5.9%)	0.17
Complex processing speed [†] (correct counts ^e)	-0.3%/ (-2.8% to 2.4%)	-3.0%/ (-4.6% to -1.3%)**	-0.9%/ (-3.4% to 1.6%)	0.08
Verbal declarative memory [†] (correct counts ^f)	-0.8%/ (-4.3% to 2.9%)	-3.7%/ (-6.1% to -1.2%)**	-1.2%/ (-4.8% to 2.5%)	0.16
Non-verbal reasoning [†] (correct counts ^g)	0.4%/ (-3.0% to 3.8%)	-2.3%/ (-4.4% to -0.2%)*	0.2%/ (-3.2% to 3.7%)	0.22

Notes: SDOH: social determinants of health, MRI: magnetic resonance imaging, C.I.: confidence interval, SD: standard deviation, [§]: linear regression model used to compute the β , [¶]: generalized linear model with gamma distribution and log link used to compute the β , [†]: Negative binomial regression with log link used to compute the β , ^a: trail making test A (TMT-A) measures processing speed and attention. ^b: trail making test B (TMT-B) assesses executive function (task-switching), often quantified as TMT-B minus TMT-A to isolate executive function. ^c: a total of 13 questions were asked from fluid intelligence test (data range from 0 to 13), ^d: maximum digits remembered correctly from numeric memory test (data range from 2 to 12), ^e: a total number of symbol digit matches made correctly from symbol-digit test within one minute (data range from 0 to 38), ^f: a total number of word pairs correctly associated from paired associate learning (data range from 0 to 10), ^g: a total number of puzzles correctly solved in matrix test (data range from 0 to 15). Model adjusted for age, sex (in the overall group only), race, smoking status, alcohol consumption, total cholesterol, physically active, body mass index, hemoglobin A1C level, depression, and Alzheimer's disease polygenic risk score, * <0.05, ** <.001.

Supplementary Table 7. Competing risk analysis between death and dementia/MCI for type 2 diabetes participants from the UK Biobank under different level of SDOH.

Notes: age, sex, and race, smoking status, alcohol consumption, physical activity, years on T2D, diabetes medications, hemoglobin A1C level, depression, total cholesterol, and AD PRS are included in the fully adjusted model. Fav.: favorable, Med.: medium, Unfav.: unfavorable, SDOH: social determinants of health, MCI: mild cognitive impairment, AD PRS: Alzheimer’s disease polygenic risk score, HR: hazard ratio, CI: confidence interval, VS: versus, *<0.05, ** < 0.01, ***<0.001, ****<0.0001.

Supplementary Table 8. Competing risk analysis between death and dementia/MCI for euglycemic participants from the UK Biobank under different level of SDOH.

Notes: age, sex, and race, smoking status, alcohol consumption, physical activity, hemoglobin A1C level, depression, total cholesterol, and AD PRS are included in the fully adjusted model. Fav.: favorable, Med.: medium, Unfav.: unfavorable, SDOH: social determinants of health, MCI: mild cognitive impairment, AD PRS: Alzheimer’s disease polygenic risk score, HR: hazard ratio, CI: confidence interval, VS: versus, *<0.05, ** < 0.01, ***<0.001, ****<0.0001.

Supplementary Table 9. Assessment of social determinants of health (SDOH) score in people with type 2 diabetes from the UK Biobank (n=21,969).

Domain	Code	Definition	Missing, n/(%)
Economic stability			
Household income	0	Average total household income before tax $\geq$ 31,000 pounds	3,967/(18.1)
	1	Average total household income before tax $<$ 31,000 pounds	
Employment status	0	Employed, retired or student	2,512/(11.4)
	1	Unemployed	
Income quality	0	Below the median of income deprivation score	540/(2.5)
	1	Above the median of income deprivation score	
Education access and quality			
Education attainment	0	Highest education level $\geq$ college	412/(1.8)
	1	Highest education level $<$ college	
Area-level education deprivation	0	Below the median of education deprivation score	540/(2.5)
	1	Above the median of education deprivation score	
Health care access and quality			
Health care access	0	Below the median of healthcare deprivation score	540/(2.5)
	1	Above the median of healthcare deprivation score	
Neighborhood and built environment			
Home ownership	0	Own home outright	771/(3.5)
	1	Rent or other arrangement	
Local crime rate	0	Below the median of crime score	1,635/(7.4)
	1	Above the median of crime score	
Natural environment	0	Above the median percentage of home location buffer classed as natural land	177/(0.8)
	1	Below the median percentage of home location buffer classed as natural land	
Social and community context			
Marital status	0	Married, living with partner	277/(1.3)
	1	Living alone	
Social support	0	Able to confide in anyone close to you at least once a week	1,175/(5.4)
	1	Confide in anyone close to you less than once a week	
Social activity	0	Attend any group activities once a week or more than once a week	143/(0.7)
	1	Attend any group activities less than once a week	
Social isolation	0	Visit friends/family or have them visit you once a week or more than once a week	376/(1.37)
	1	Visit friends/family or have them visit you less than once a week	
Loneliness	0	Participants do not feel lonely	475/(2.16)
	1	Participants do feel lonely	
Perceived stress	0	None	412/(1.9)
	1	Experienced illness, injury, bereavement, stress within last 2 years	
Race/ethnicity	0	White	113/(0.5)
	1	Non-white	

Supplementary Table 10. Assessment of social determinants of health (SDOH) score in people with type 2 diabetes from the AoU (n=77,082).

Domain	Code	Definition	Missing, n(%)
Economic stability			
Household income	0	Annual income $\geq$ 50K US dollars	19,389/(25.1)
	1	Annual income $<$ 50K US dollars	
Employment status	0	Employed, self-employed, student, retired	2,409/(3.1)
	1	Out of work, unable to work, homemaker	
Food insecurity	0	Never true	50,702/(65.7)
	1	Often true, sometimes true	
Housing instability	0	Moved $<$ 2 times in last 12 months	51,448/(66.7)
	1	Moved $\geq$ 2 times in last 12 months	
Stable house concern	0	No worried or concerned about not having a place to live in the past 6 months	1,474/(1.9)
	1	Worried or concerned about not having a place to live in the past 6 months	
Education access and quality			
Education attainment	0	High school or above	2,061/(2.6)
	1	Les than school	
Health care access and quality			
Discrimination in medical settings	0	Never reported any discrimination frequency out of 7 questions	51,457/(66.7)
	1	Ever reported any discrimination frequency other than never out of 7 questions	
Needs help reading health-related materials	0	Participants answered never to the question	14,321(18.5)
	1	Any other answers expect never to the question	
Confidence in filling out medical forms	0	Participants answered extremely or quite a bit	1,717/(2.2)
	1	Participants answered somewhat, a little bit or not at all	
Neighborhood and built environment			
Home ownership	0	Own a home/house	3,173/(4.1)
	1	Rent or other arrangement	
Local crime rate	0	Mean crime safety score $<$ 3	54,424/(70.6)
	1	Mean crime safety score $\geq$ 3	
Neighborhood disorder [§]	0	Mean disorder score $<$ 3	55,348/(71.8)
	1	Mean disorder score $\geq$ 3	
Neighborhood walkability	0	Mean walkability score $\geq$ 2.5	50,917/(66.0)
	1	Mean walkability score $<$ 2.5	
Neighborhood residential density	0	Other housing type	69,656/(90.3)
	1	Housing type as detached single family or duplex/town house	
Social and community context			
Marital status	0	Married, living with partner	5,355/(6.9)
	1	Never married, divorced, widowed, separated	
Social support	0	Combined social support score $\geq$ 50	52,804/(68.5)
	1	Combined social support score $<$ 50	
Loneliness	0	Mean loneliness score that closer to 1	52,671/(68.3)
	1	Mean loneliness score that closer to 4	
Social cohesion	0	Combined social cohesion score $\geq$ 3	51,885/(67.3)
	1	Combined social cohesion score $<$ 3	
Perceived stress	0	Total perceived stress score $<$ 75 percentile	54,901/(71.2)
	1	Total perceived stress score $\geq$ 75 percentile	
Daily spiritual experiences	0	Above the mean spirituality score	53,367/(69.2)
	1	Below the mean spirituality score	
Everyday discrimination	0	Overall frequency of everyday discrimination with mean that closer to 1	53,186/(69.0)
	1	Overall frequency of everyday discrimination with mean that closer to 6	

[§]Combination of physical and social disorder. Notes: AoU: All of Us, 0: advantage, 1: disadvantage.

Supplementary Table 11. Field ID and Observational Medical Outcomes Partnership concept ID that are used to access social determinants of health variables from two cohorts.

Variable name	The UK Biobank	AoU
	Field ID	Observational Medical Outcomes Partnership concept ID
Economic stability		
Household income ^a	738	1585375
Employment status ^b	6142	1585952
Income quality ^c	26411, 26418, 26428	NA
Food insecurity ^d	NA	40192426, 40192517
Housing instability ^d	NA	40192441
Stable house concern ^d	NA	1585886
Education access and quality		
Education attainment ^a	6138	1585940
Area-level education deprivation ^c	26414, 26421, 26431	NA
Health care access and quality		
Health care access ^c	26413, 26420, 26430	NA
Discrimination in medical settings ^d	NA	40192383, 40192394, 40192423, 40192425, 40192497, 40192503, 40192505
Needs help reading health-related materials ^d	NA	NA
Confidence in filling out medical forms ^d	NA	1585710 [§]
Neighborhood and built environment		
Home ownership ^a	680	1585370
Local crime rate ^b	26416	40192414, 40192492
Natural environment ^c	24506	NA
Neighborhood disorder ^{§,d}	NA	40192420, 40192522, 40192412, 40192469, 40192456, 40192386, 40192456, 40192386, 40192500, 40192493, 40192457, 40192476, 40192404, 40192400, 40192384, 40192400, 40192384
Neighborhood walkability ^d	NA	40192431, 40192436, 40192437, 40192440, 40192430, 903096, 1177221, 40192520
Neighborhood residential density ^d	NA	45877171, 1035245, 45878935, 45883274, 45879538
Social and community context		
Marital status ^a	709	1585892
Social support ^b	2110	40192388, 40192399, 40192439, 40192442, 40192446, 40192480, 40192511, 40192528
Social activity ^c	6160	NA
Social isolation ^c	1031	NA
Perceived stress ^b	6145	40192381, 40192396, 40192419, 40192445, 40192449, 40192452, 40192462, 40192491, 40192506, 40192525
Loneliness ^b	2020	40192390, 40192397, 40192398, 40192494, 40192501, 40192504, 40192507, 40192516
Social cohesion ^d	NA	40192463, 40192411, 40192499, 40192417
Daily spiritual experiences ^d	NA	40192401, 40192415, 40192443, 40192471, 40192475, 40192498
Everyday discrimination ^d	NA	40192380, 40192395, 40192416, 40192451, 40192466, 40192489, 40192490, 40192496, 40192519
Race/ethnicity ^c	21000	NA

[§]Combination of physical and social disorder. Notes: AoU: All of Us, NA: not applicable. For SDOH components harmonization, the superscript in each SDOH components represent a: directly comparable, b: nearly comparable, c: approximated, c: UKB only variable, d: AoU only variable.

Supplementary Table 12. Impute missing social determinants of health (SDOH) variables with multivariate imputation by chained equations (MICE) or probabilistic principal component analysis (PPCA) for type 2 diabetes participants from All of Us (n=13300).

Step	Protocol Detail
1	Select MICE as main imputation tool [1] and choose PPCA as validation approach [2].
2	In MICE, only SDOH variables (model 1) or SDOH variables plus demographic variables: sex, age, and race (model 2) were used for imputation. However, only SDOH variables were used in PPCA (model 3).
3	Chose masked cell rate a 10% to compare the prediction accuracy between MICE and PPCA.
4	Compare the raw distribution versus whole distribution after imputation for each SDOH variables.

The benchmark imputation comparison results are given as:

Model	Percentage of correct imputation	RMSE	Number of categorical cells	Number of numerical cells
Model 1	68.3	1.28	6,887	5,244
Model 2	64.8	1.28	6,887	4,930
Model 3	76.1	0.95	6,887	5,244

Notes: RMSE: root-mean-square error. Overall, MICE yielded 68.3% prediction accuracy versus PPCA at 76.1%. We further checked the distribution of binary SDOH variables before and after imputation, average shifts are 0.0146, 0.0201 when handling the binary variables, or 0.0956, 0.0227 when dealing with continuous variables, for MICE and PPCA, respectively. Such shift distributions on SDOH variables could because the nature of missingness from cross-sectional survey data [3]. Although PPCA might have slightly better prediction performance than MICE, we picked imputation results from MICE over PPCA to better respect survey measurement scales and design [4].

Supplementary Table 13. Steps to compute Alzheimer’s disease (AD) polygenic risk score (PRS) for AoU participants.

Step	Description	Pipeline Detail
1	Downloading PRS weight	Download PRS weight: download the late-onset AD PRS file PGS000334 [5] from Polygenic Score Catalog website (https://www.pgscatalog.org/) [6]. This score includes 22 variants and was originally derived using a clumping and thresholding approach.
2	Match variants to genotype data	Matched the score variants to the imputed genotype data.
3	Harmonize alleles	Harmonized alleles so that the genotype dosage corresponded to the reported effect allele.
4	Handle strand ambiguity	Excluded palindromic variants with intermediate/high allele frequency to minimize strand ambiguity.
5	PRS computing	Calculated AD PRS for each participant as weighted sum of effect allele dosages multiplied by the published sample size.
6	Standardization	Conduct Z-score transformation on calculated AD PRS for downstream analyses [7].

Notes, AoU: All of Us.

Supplementary Table 14. International Classification of Diseases (ICD) and procedures codes used to ascertain incident outcomes in the UKB.

Outcome	ICD 9 codes	ICD 10 codes
Type 1 diabetes	250.00, 250.02, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92	E10.0, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E10.9
Type 2 diabetes	250.00, 250.02, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92	E11, E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.8, E11.9
Depression	296.0, 296.1, 296.2, 296.3	F32.0, F32.1, F32.2, F32.3, F32.8, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, F33.8, F33.9, F34.0, F34.1
Dementia	290.0, 290.1, 290.2, 290.3, 290.4, 290.9, 294.1, 294.2, 294.8, 294.9, 331.0, 331.1, 331.2, 331.8, 331.9, 331.5	G30, G30.0, G30.1, G30.8, G30.9, G31.0, G31.1, G31.8, F00, F00.0, F00.1, F00.2, F00.9, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, A81.0, I67.3
Alzheimer's disease	331.0	G30, G30.0, G30.1, G30.8, G30.9, F00, F00.0, F00.1, F00.2, F00.9
Vascular dementia	290.4	F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
Mild cognitive impairment	331.8	F06.7, F07.8, F09, G31.8, R41.3, R41.8

Supplementary Table 15. Source of Information for MRI neuroimaging measures and the cognitive test measures in the UKB.

Neuroimaging by MRI	Field ID
T1-based head size scaling factor [†]	25000
Total brain volume	25009
White matter volume	25007
Grey matter volume	25005
Left Hippocampus volume [§]	25019
Right hippocampus volume [§]	25020
White matter hyperintensities volume [§]	25781
Cognitive test	
Trail making test A	6348
Trail making test B	6350
Verbal/numerical reasoning	20016
Working memory binary	4282
Complex processing speed linear	23324
Verbal declarative memory	20197
Non-verbal reasoning	6373

Notes: the brain magnetic resonance imaging (MRI) used standardized protocols on Siemens Skyra 3T scanners to acquire structural, diffusion, and functional images. Brain function variables included total brain volume, white matter volume, grey matter volume, left hippocampal volume, right hippocampal volume, and white matter hyperintensity volume (standardized by T1-based head size scaling factor). Cognitive test measures included executive function (trail making test A), executive function (trail making test B), verbal & numerical reasoning (fluid intelligence), working memory (backward digit span task), complex processing speed (symbol digit substitution), verbal declarative memory (paired associate learning), and non-verbal reasoning (matrix pattern completion). UKB: the UK Biobank. [§]: Normalized by multiplying the T1-based head size scaling factor, [†]: standardizing factor used for white matter hyperintensities volume.

Supplementary Table 16. Observational Medical Outcomes Partnership (OMOP) concept ID used to retrieve phenotyping data from AoU.

Variable name	Data type	Source	OMOP concept ID
Sex	Surveys	The Basics	1585845
Race/ethnicity	Surveys	The Basics	1586140
Education	Surveys	The Basics	1585940
Smoking status	Surveys	Lifestyle	1585857
Alcohol consumption	Surveys	Lifestyle	1586198
Body height	EHR	L&M	3036277
Body weight	EHR	L&M	3025315
Hemoglobin A1c	EHR	L&M	3000963
Blood glucose	EHR	L&M	3004501
Type 1 diabetes	Surveys	PFHH	43529923
Type 2 diabetes	Surveys	PFHH	43529932
Depression	EHR	Conditions	440383
Dementia	EHR	Conditions	4182210
Alzheimer's disease	EHR	Conditions	378419
Mild cognitive impairment	EHR	Conditions	4297400

Notes: EHR: electronic health records, L&M: Labs & Measurement, PFHH: personal and family health history, AoU: All of Us.

Supplementary Table 17. Observational Medical Outcomes Partnership (OMOP) Concept ID used to retrieve prescription for type 2 diabetes medications from AoU.

Medication name	Data type	Source	OMOP Concept ID
Biguanides	EHR	Drug exposures	40164929, 40164897, 40163924, 1503297, 40164930, 40164898, 40163926, 40164946, 40163928, 40220373
Sulfonylureas	EHR	Drug exposures	19077638, 19077636, 1560171, 19079990, 19080793, 19077637, 1597772, 1597773, 1597761, 1597757, 1597756, 1597760, 1597759, 19126618, 19077682, 19077659, 1559684, 1559685, 1594973, 1502855, 1502856, 1502809
Meglitinides	EHR	Drug exposures	19023424, 19023425, 19023426, 1502830, 1502826, 1502829
Alpha-glucosidase inhibitors	EHR	Drug exposures	19023063, 1529352, 1529331, 19021312
Thiazolidinediones	EHR	Drug exposures	1525221, 19079293, 1525220, 1525215, 1525216, 1525217, 1525218, 19079465, 1547504, 1547510, 1547506, 1547505, 1547508
DPP-4 inhibitors	EHR	Drug exposures	19125043, 19125041, 19125049, 19125051, 1580747, 19125045, 19125047, 40166041, 40166037, 40166042, 40166035, 40166038, 43013924, 43013911, 43013928, 43013884, 43013925, 43013896, 43013912, 40239219, 40239218, 40239216
SGLT-2 inhibitors	EHR	Drug exposures	43526467, 43526468, 43526472, 43526471, 43526465, 45774714, 45774721, 1718898, 1718899, 1718901, 44785831, 44785473, 44785477, 44785833, 44785829, 45775455, 45775621, 45775860, 45775999, 793826, 45774754, 45774758, 45774893, 45774895, 45774751, 46287691, 1592794, 1592795, 46287410, 1592798, 793327, 793331, 793321, 793329, 793293, 793300
GLP-1 receptor agonists	EHR	Drug exposures	1583722, 45774533, 1583729, 45774531, 1583730, 1583727, 793114, 19135405, 42708078, 42708079, 793111, 42902866, 40169222, 40169223, 45892686, 40170911, 1718711, 42902992, 1718706, 40170912, 42903382, 45774442, 45774448, 45774446, 45774438, 37003607, 45774435, 37003609, 37003606, 37003608, 44057249, 1718604, 1718599, 40220862, 40221118, 44506754, 793152, 793147, 793143, 37003617, 37003616, 741834, 793154, 1537597, 780249, 1537599, 793153, 1537596, 37496842, 1537601, 1537603, 741832, 37496746, 37496844, 37496840, 1537598, 1537605, 780248, 1537602, 1537600, 1537604, 37496838, 37496832, 780260, 780256, 780266, 779705, 780262, 780259, 780255, 780264, 780258, 780265, 780261, 780257, 780263
Dopamine-2 agonist	EHR	Drug exposures	730551, 730548, 19007101, 730572, 19006288, 19083957
Insulin	EHR	Drug exposures	19058398, 19078555, 19078559, 19078558, 1502910, 46234049, 19135276, 1550023, 19078557, 40166274, 19078632, 19071700, 46233969, 1567198, 1502905, 46233970, 46234047, 19078552, 19078554, 35604094, 1567232, 1596977, 1516978, 19123376, 1516981, 19012266, 1146756, 19078551, 1516979, 19078603, 46221557, 1146285

Notes: EHR: electronic health records.

Supplementary Table 18. Application of elastic-net Cox regression to construct the weighted SDOH score.

Step	Protocol Detail
1	Prepare a pool of SDOH variables for selection and weighting.
2	Include major demographic and clinical factors: age, sex, race/ethnicity, body mass index, hemoglobin A1C, depression, smoking status, and drinking status into elastic-net model as covariable.
3	Training the elastic net coefficients from participants with complete data from the candidate predictors.
4	Construct the model matrix with all SDOH variables and covariates.
5	Select and shrinking predictors using penalized Cox regression, with elastic tuning parameter: $\alpha = 0.05$, n-fold = 10
6	The tuning parameter was selected using lambda.min
7	Extract the coefficient that matched to SDOH variables
8	Select the SDOH variable with nonzero elastic-net Cox coefficients as final weighted score
9	Calculate the coefficient with preserve direction and magnitude of the association, then calculated the denominator as sum of nonzero signed β s.
10	Standardized the participant-level raw weighted SDOH score

The formula used to compute weighted SDOH score as:

$$\text{Weighted SDOH score}_i = \left(\sum_{j=1}^n \beta_j X_{ij} \right) \times \frac{n}{\sum_{j=1}^n \beta_j}$$

Where:

X_{ij} : Value of SDOH indicator j for participant i

β_j : Elastic-net Cox coefficient for SDOH indicator j

n : Number of SDOH indicators with nonzero elastic-net coefficients

Supplementary Table 19. UKB sensitivity analysis for age < 65 years old.

	Dementia					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	P-interaction	Ptrend	HR (95%CI)	P-interaction	Ptrend
All		0.03	<0.001		0.21	0.02
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.45 (0.75, 2.83)			2.25 (0.93, 5.43)		
Unfavorable	3.53 (1.94, 6.41)			2.66 (1.13, 6.24)		
Per 1-point increment	1.76 (1.38, 2.26)	0.03		1.49 (1.11, 2.01)	0.21	
Men			0.004			0.25
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.14 (0.55, 2.39)			1.77 (0.70, 4.46)		
Unfavorable	2.44 (1.28, 4.66)			1.76 (0.71, 4.34)		
Per 1-point increment	1.58 (1.20, 2.07)			1.36 (0.98, 1.90)		
Women			0.003			0.15
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	5.74 (0.70, 47.30)			N.A.		
Unfavorable	11.86 (1.56, 90.34)			N.A.		
Per 1-point increment	3.19 (1.46, 6.99)			2.18 (1.07, 4.46)		
	Mild Cognitive Impairment					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	P-interaction	Ptrend	HR (95%CI)	P-interaction	Ptrend
All		0.60	0.64		0.93	0.18
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.01 (0.57, 1.80)			1.20 (0.58, 2.50)		
Unfavorable	1.14 (0.64, 2.01)			1.57 (0.79, 3.13)		
Per 1-point increment	1.11 (0.88, 1.39)	0.60		1.11 (0.84, 1.45)	0.93	
Men			0.95			0.12
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	0.49 (0.22, 1.11)			2.31 (0.89, 6.02)		
Unfavorable	1.00 (0.51, 1.94)			2.23 (0.86, 5.80)		
Per 1-point increment	1.04 (0.78, 1.40)			1.13 (0.81, 1.57)		
Women			0.94			0.9
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	2.17 (0.82, 5.75)			0.28 (0.06, 1.38)		
Unfavorable	1.18 (0.42, 3.35)			1.01 (0.36, 2.86)		
Per 1-point increment	1.10 (0.74, 1.64)			1.09 (0.67, 1.80)		

Supplementary Table 20. UKB sensitivity analysis for age ≥ 65 years old.

	Dementia					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All		0.52	0.01		0.38	0.05
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.03 (0.63, 1.67)			1.76 (0.97, 3.18)		
Unfavorable	1.70 (1.07, 2.71)			1.83 (1.01, 3.33)		
Per 1-point increment	1.25 (1.01, 1.55)	0.16		1.39 (1.08, 1.80)	0.5	
Men			0.18			0.06
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	0.90 (0.50, 1.63)			2.08 (1.03, 4.22)		
Unfavorable	1.41 (0.83, 2.39)			1.98 (0.98, 3.99)		
Per 1-point increment	1.17 (0.91, 1.49)			1.47 (1.10, 1.97)		
Women			0.03			0..87
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.04 (0.43, 2.50)			0.81 (0.24, 2.68)		
Unfavorable	2.27 (1.02, 5.07)			1.08 (0.36, 3.20)		
Per 1-point increment	1.62 (0.97, 2.72)			1.14 (0.68, 1.94)		
	Mild Cognitive Impairment					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All		0.92	0.22		0.48	0.65
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.69 (0.86, 3.33)			1.20 (0.61, 2.35)		
Unfavorable	1.60 (0.79, 3.23)			1.17 (0.60, 2.30)		
Per 1-point increment	1.26 (0.93, 1.71)	0.92		1.03 (0.77, 1.36)	0.48	
Men			0.21			0.96
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.47 (0.66, 3.29)			1.66 (0.78, 3.53)		
Unfavorable	1.63 (0.77, 3.47)			1.04 (0.46, 2.34)		
Per 1-point increment	1.24 (0.89, 1.74)			0.97 (0.71, 1.33)		
Women			0.51			0.36
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.28 (0.37, 4.40)			0.94 (0.18, 4.85)		
Unfavorable	1.53 (0.42, 5.51)			1.80 (0.43, 7.43)		
Per 1-point increment	1.38 (0.69, 2.77)			1.22 (0.62, 2.43)		

Supplementary Table 21. AoU sensitivity analysis for age < 65 years old.

	Dementia					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All		0.57	<0.001		0.41	0.01
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	7.49 (0.91, 61.48)			N.A.		
Unfavorable	18.21 (2.32, 142.61)			N.A.		
Per 1-point increment	2.54 (1.68, 3.84)	0.86		12.36 (2.95, 51.79)	0.69	
Men			0.02			0.94
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	N.A.			N.A.		
Unfavorable	N.A.			N.A.		
Per 1-point increment	2.97 (1.47, 6.02)			21.29 (1.43, 317.73)		
Women			0.008			0.99
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	3.94 (0.44, 35.64)			N.A.		
Unfavorable	11.00 (1.34, 89.95)			N.A.		
Per 1-point increment	2.42 (1.45, 4.04)			8.03 (1.70, 38.00)		
	Mild Cognitive Impairment					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All		0.42	0.13		0.76	0.04
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.09 (0.78, 1.52)			1.63 (0.88, 3.01)		
Unfavorable	1.30 (0.92, 1.82)			1.87 (1.04, 3.36)		
Per 1-point increment	1.11 (0.97, 1.26)	0.21		1.27 (1.00, 1.62)	0.59	
Men			0.84			0.19
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	0.92 (0.49, 1.72)			2.22 (0.58, 8.49)		
Unfavorable	0.94 (0.48, 1.82)			2.49 (0.67, 9.27)		
Per 1-point increment	0.98 (0.76, 1.27)			1.37 (0.84, 2.26)		
Women			0.05			0.12
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.14 (0.77, 1.69)			1.48 (0.75, 2.92)		
Unfavorable	1.47 (0.99, 2.19)			1.71 (0.88, 3.33)		
Per 1-point increment	1.16 (1.00, 1.36)			1.23 (0.93, 1.62)		

Supplementary Table 22. AoU sensitivity analysis for age ≥ 65 years old.

	Dementia					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All		0.26	<0.001		1	1
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	2.28 (1.21, 4.31)			N.A.		
Unfavorable	4.86 (2.67, 8.86)			N.A.		
Per 1-point increment	2.13 (1.73, 2.63)	0.77		N.A.	1	
Men			<0.001			1
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.41 (0.59, 3.36)			N.A.		
Unfavorable	4.15 (1.94, 8.89)			N.A.		
Per 1-point increment	2.17 (1.61, 2.91)			N.A.		
Women			<0.001			1
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	3.87 (1.44, 10.43)			N.A.		
Unfavorable	5.97 (2.24, 15.96)			N.A.		
Per 1-point increment	2.11 (1.56, 2.85)			N.A.		
	Mild Cognitive Impairment					
	Type 2 Diabetes			Euglycemic		
SDOH	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All		0.93	<0.001		0.13	0.14
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.60 (1.15, 2.22)			2.02 (0.69, 5.96)		
Unfavorable	1.83 (1.30, 2.58)			2.28 (0.77, 6.73)		
Per 1-point increment	1.24 (1.07, 1.44)	0.77		1.35 (0.83, 2.18)	0.03	
Men			0.004			0.08
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.69 (1.02, 2.82)			3.83 (0.44, 33.38)		
Unfavorable	2.15 (1.28, 3.60)			5.93 (0.70, 50.17)		
Per 1-point increment	1.29 (1.04, 1.60)			2.73 (1.04, 7.18)		
Women			0.06			0.36
Favorable	1.00 (Ref)			1.00 (Ref)		
Medium	1.53 (1.00, 2.34)			0.83 (0.23, 3.05)		
Unfavorable	1.56 (0.98, 2.47)			0.72 (0.19, 2.79)		
Per 1-point increment	1.21 (1.00, 1.47)			0.91 (0.52, 1.61)		

Supplementary Table 23. UKB sensitivity analysis for dementia (after exclude dementia case at the first three years after enrolment).

Type 2 Diabetes				
SDOH	Case/Pop.	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All			0.02	<.001
Favorable	42/3110	1.00 (Ref)		
Medium	66/3047	1.42 (0.92, 2.17)		
Unfavorable	119/3284	2.46 (1.65, 3.68)***		
Per 1-point increment		1.48 (1.25, 1.76)***	0.01	
Men				0.008
Favorable	31/2071	1.00 (Ref)		
Medium	38/1672	1.36 (0.81, 2.26)		
Unfavorable	82/2600	1.81 (1.15, 2.83)*		
Per 1-point increment		1.34 (1.11, 1.62)**		
Women				<.001
Favorable	8/1055	1.00 (Ref)		
Medium	13/763	2.34 (0.72, 7.65)		
Unfavorable	55/1280	6.64 (2.34, 18.84)***		
Per 1-point increment		2.28 (1.45, 3.59)***		
Euglycemic				
SDOH	Case/Pop.	HR (95%CI)	<i>P</i> -interaction	<i>P</i> trend
All			0.27	0.001
Favorable	20/3793	1.00 (Ref)		
Medium	53/3827	2.57 (1.45, 4.55)**		
Unfavorable	65/3771	2.62 (1.49, 4.61)***		
Per 1-point increment		1.42 (1.17, 1.72)***	0.3	
Men				0.006
Favorable	18/2407	1.00 (Ref)		
Medium	32/2592	1.73 (0.91, 3.29)		
Unfavorable	48/2487	2.29 (1.25, 4.21)**		
Per 1-point increment		1.35 (1.09, 1.66)**		
Women				0.13
Favorable	5/1314	1.00 (Ref)		
Medium	14/1303	2.27 (0.72, 7.16)		
Unfavorable	21/1288	2.51 (0.81, 7.76)		
Per 1-point increment		1.69 (1.08, 2.64)*		

Notes: Pop.: population.

Supplementary Table 24. UKB sensitivity analysis for MCI (after exclude MCI case at the first three years after enrolment).

Type 2 Diabetes				
SDOH	Case/Pop.	HR (95%CI)	P-interaction	Ptrend
All			0.29	0.4
Favorable	36/3113	1.00 (Ref)		
Medium	51/3069	1.25 (0.79, 1.97)		
Unfavorable	63/3304	1.23 (0.78, 1.96)		
Per 1-point increment		1.12 (0.93, 1.36)	0.5	
Men				0.89
Favorable	27/2072	1.00 (Ref)		
Medium	22/1680	0.92 (0.52, 1.65)		
Unfavorable	45/2610	0.96 (0.57, 1.62)		
Per 1-point increment		1.07 (0.85, 1.34)		
Women				0.13
Favorable	12/1057	1.00 (Ref)		
Medium	11/775	1.20 (0.48, 3.00)		
Unfavorable	33/1292	1.74 (0.80, 3.77)		
Per 1-point increment		1.24 (0.87, 1.76)		
Euglycemic				
SDOH	Case/Pop.	HR (95%CI)	P-interaction	Ptrend
All			0.08	0.28
Favorable	25/3795	1.00 (Ref)		
Medium	39/3830	1.24 (0.73, 2.11)		
Unfavorable	46/3783	1.33 (0.80, 2.22)		
Per 1-point increment		1.18 (0.96, 1.45)	0.09	
Men				0.97
Favorable	18/2410	1.00 (Ref)		
Medium	33/2589	1.41 (0.78, 2.54)		
Unfavorable	30/2502	1.05 (0.57, 1.93)		
Per 1-point increment		1.08 (0.86, 1.36)		
Women				0.05
Favorable	6/1316	1.00 (Ref)		
Medium	6/1302	0.59 (0.16, 2.24)		
Unfavorable	17/1289	2.22 (0.78, 6.33)		
Per 1-point increment		1.72 (1.05, 2.81)*		

Notes: Pop.: population.

Supplementary Table 25. Social determinants of health categories by baseline age group in the two study cohorts.

UKB T2D						
	Men			Women		
Age, mean/SD/Prev., (year)	<55	55-65	65 and plus	<55	55-65	65 and plus
Favorable	49.3/3.9/55.9	59.8/2.7/50.0	66.8/1.5/31.2	49.4/3.7/56.5	59.5/2.8/35.6	66.9/1.5/18.6
Medium	49.5/3.7/8.9	60.5/2.7/11.9	67.0/1.5/15.9	49.6/3.7/7.0	60.9/2.5/22.1	67.0/1.4/34.1
Unfavorable	49.1/3.8/35.2	60.6/2.7/38.1	67.0/1.5/52.9	49.3/3.8/36.5	60.6/2.6/42.3	66.9/1.5/47.3
UKB Euglycemic						
	Men			Women		
Age, mean/SD/Prev., (year)	<55	55-65	65 and plus	<55	55-65	65 and plus
Favorable	49.5/3.7/29.3	59.7/2.8/23.6	66.8/1.5/16.4	49.5/3.5/43.7	59.5/2.8/31.0	66.9/1.5/19.0
Medium	49.3/3.8/51.9	60.1/2.8/51.9	67.0/1.5/49.7	49.4/3.8/38.5	60.1/2.7/41.9	66.9/1.4/44.0
Unfavorable	48.9/3.9/18.7	60.7/2.6/24.5	67.0/1.5/33.9	49.2/3.8/17.7	60.5/2.7/27.2	67.1/1.5/36.9
AoU T2D						
	Men			Women		
Age, mean/SD/Prev., (year)	<55	55-65	65 and plus	<55	55-65	65 and plus
Favorable	45.9/6.3/27.9	60.0/3.0/30.0	75.4/6.4/35.8	45.0/6.7/33.8	60.0/2.9/33.2	73.9/6.0/33.2
Medium	45.8/6.7/32.6	60.0/2.9/30.4	75.6/6.5/34.6	44.6/7.0/33.5	59.8/2.9/31.1	74.6/6.4/34.3
Unfavorable	45.9/6.6/39.5	60.1/2.9/39.6	74.0/6.7/29.6	44.6/7.3/32.6	59.9/2.8/35.7	73.7/6.5/32.5
AoU Euglycemic						
	Men			Women		
Age, mean/SD/Prev., (year)	<55	55-65	65 and plus	<55	55-65	65 and plus
Favorable	39.8/8.3/28.0	59.9/2.9/33.2	74.8/6.8/38.8	39.2/8.4/29.4	59.7/2.9/29.7	75.3/6.6/40.8
Medium	40.9/7.8/32.0	59.8/2.9/31.2	75.3/6.6/35.8	40.4/7.7/32.5	59.7/2.9/30.6	74.3/6.2/36.0
Unfavorable	41.2/7.5/40.0	59.6/2.9/35.6	72.9/6.1/25.4	41.2/7.5/38.1	59.6/2.9/39.7	72.0/5.7/23.1

Notes: Prev.: prevalence, T2D: type 2 diabetes, SD: standard deviation, UKB: UK Biobank, AoU: All of Us.