Supplementary appendix

Supplementary Methods 1. Urbanization level

Based on participants' self-reported residential locations in the UK Biobank, we categorized urbanization levels into four tiers (higher tiers indicating greater urbanization). The distribution of residential types is as follows:

(1) High Urbanization : Included “England/Wales - Urban – sparse”, "England/Wales - Urban - less sparse", "Scotland - Large Urban Area", and "Scotland - Other Urban Area".

(2) Moderate Urbanization: Included "England/Wales - Town and Fringe - sparse", "England/Wales - Town and Fringe - less sparse", "Scotland - Accessible Small Town", and "Scotland - Remote Small Town".

(3) Low Urbanization: Included " England/Wales - Village - sparse ", " England/Wales - Village - less sparse", "Scotland - Very Remote Small Town", and "Scotland - Accessible Rural".

(4) Very Low/Sparse Urbanization: Included " England/Wales - Hamlet and Isolated dwelling - sparse", "England/Wales - Hamlet and Isolated Dwelling - less sparse", "Scotland - Remote Rural", "Scotland - Very Remote Rural", and "Postcode not linkable".

Supplementary Methods 2. Modifiable lifestyle factors

(1) Smoking frequency: Never = 0; Occasionally = 1; Almost all day = 3.

(2) Drinking frequency: Never = 0; Special occasions only = 1; One to three times a month = 2; Once or twice a week = 3; Three or four times a week = 4; daily or almost daily = 5.

(3) Fruit and vegetable intake: the sum of normalized values (0~1) of daily cooked vegetable intake, salad / raw vegetable intake, fresh fruit intake, dried fruit intake.

(4) Meat intake: the sum of normalized values (0~1) of daily oily fish intake, non-oily fish intake, processed meat intake, poultry intake, beef intake, lamb/mutton intake, pork intake.

(5) Bread and cereal intake: the sum of normalized values (0~1) of daily bread intake and cereal intake.

Supplementary Methods 3. Relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (SI)

(1) RERI quantifies the excess risk from the interaction of two exposures beyond their independent effects. It is calculated as:

$$RERI=RR_{11}-RR_{10}-RR_{01}+1$$

where RR_{11} is the relative risk when both exposures are present, and RR_{10}, RR_{01} are the risks when only one exposure is present. RERI > 0 indicates synergistic interaction, while RERI < 0 suggests antagonism.

(2) AP represents the proportion of disease among doubly exposed individuals attributable to the interaction:

$$AP= RERI/RR_{11}$$

This metric ranges from 0 to 1, with higher values indicating a greater contribution of interaction to the risk.

(3) SI measures the relative magnitude of synergistic effects compared to independent

effects:

$$SI= RR_{11}-1/((RR_{10}-1)+(RR_{01}-1))$$

An SI > 1 implies synergy, while SI = 1 suggests additivity.

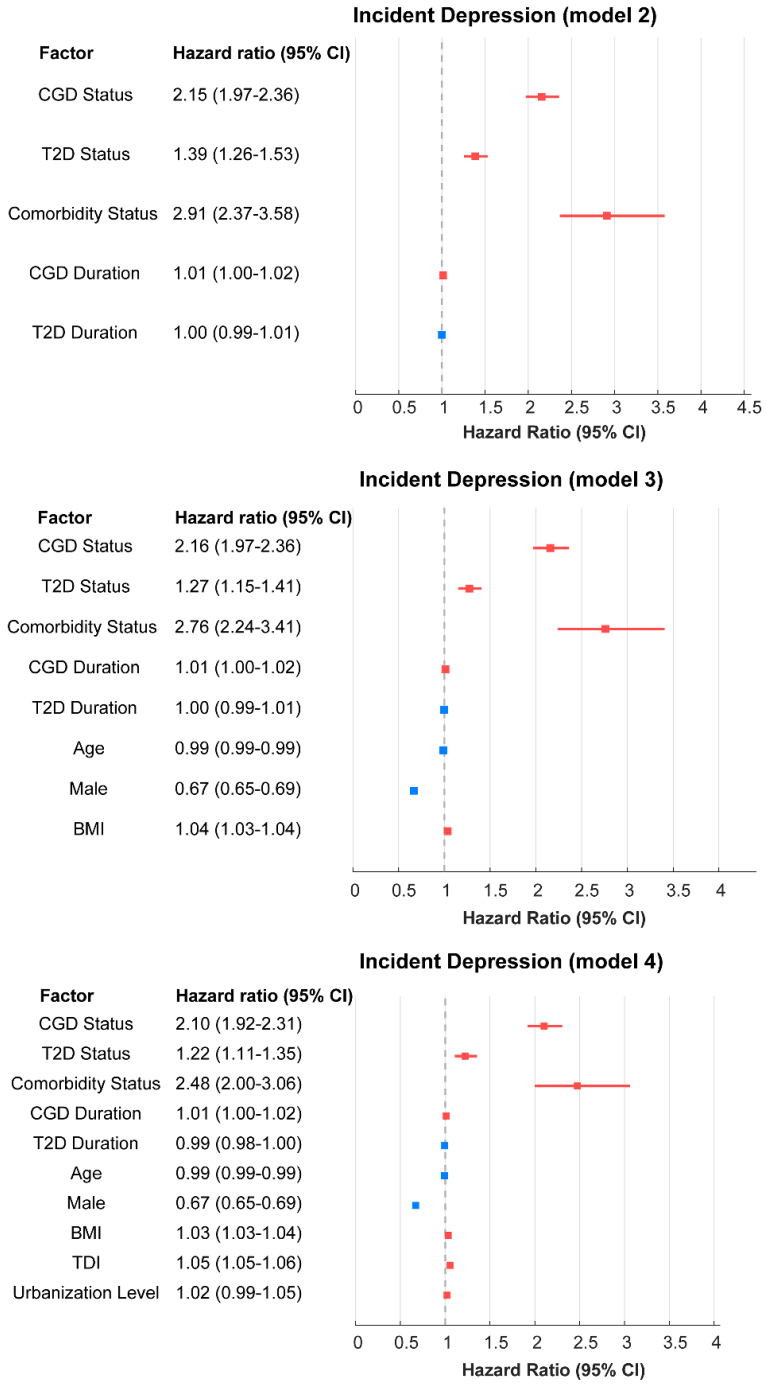
In this study, we established a logistic regression model, incorporating the risk factors and covariates, and used exp(beta value) to calculate RR values:

Depression status (0,1) = b1*COM + b2*T2D + b3*CGD + b4*T2D duration + b5*CGD duration + b6*Age + b7*Sex + b8*BMI + e

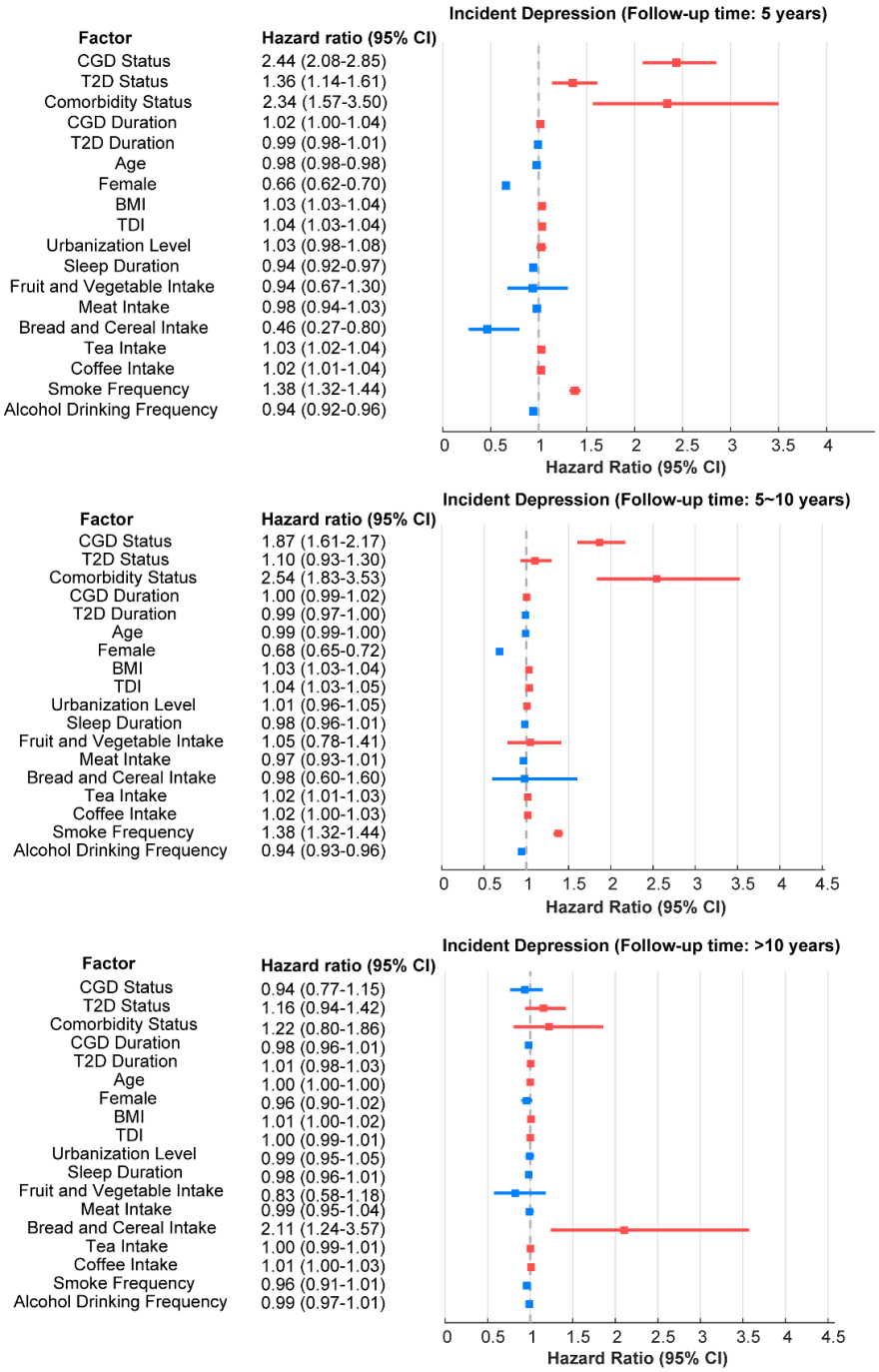
$$RR_{11} = exp^{(b1)}; RR_{10} = exp^{(b2)}; RR_{01} = exp^{(b3)}.$$

Supplementary Methods 4. Mediation analysis

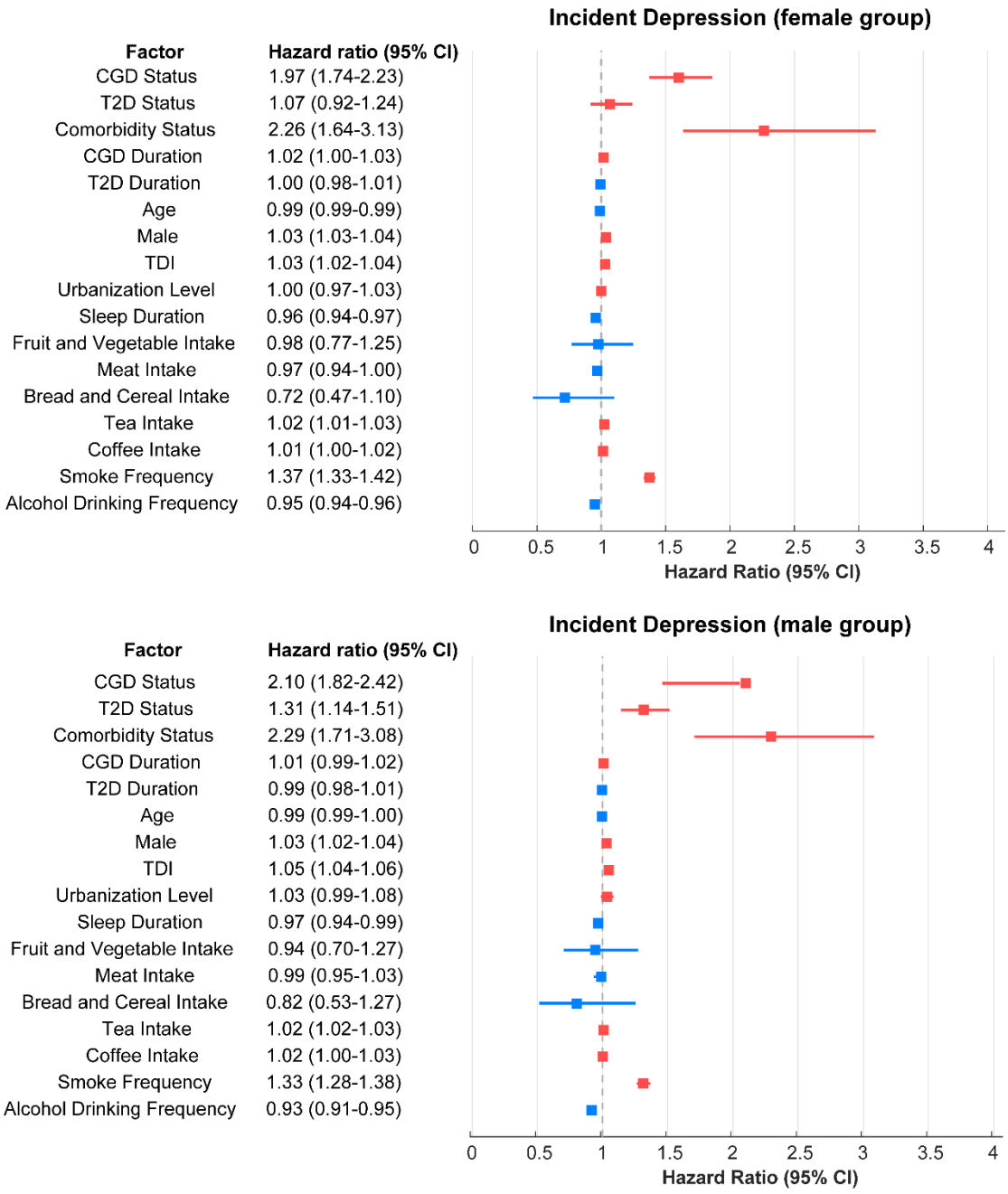
During UK Biobank's second assessment phase (Instance 2, 2014–2019), brain MRI scans were acquired for 54,060 participants. We defined T2D, CGD, and depression as pre-existing conditions prior to Instance 2.



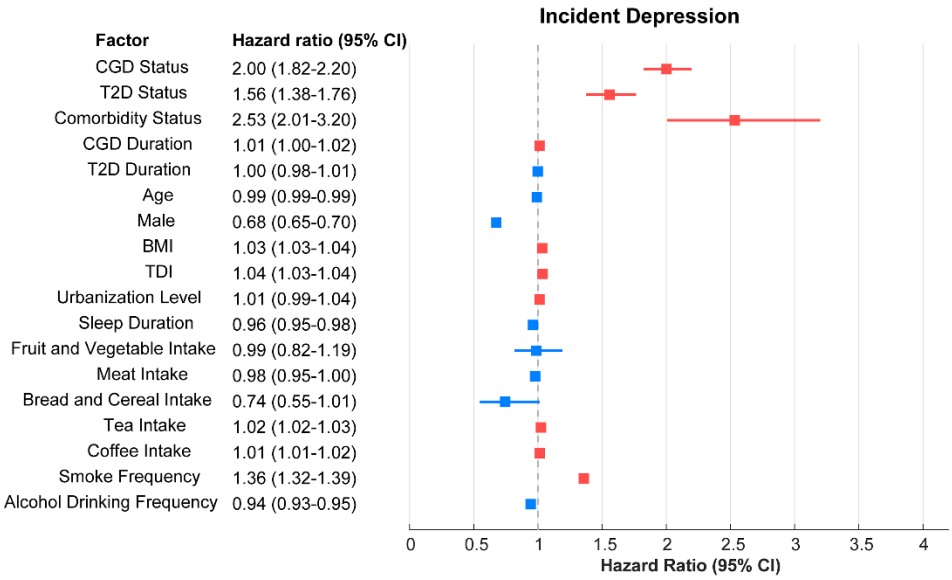
Supplementary Figure 1. Effect of T2D-CGD comorbidity on depression incidence after step-wise adjusting clinical (model 2), demographical (model 3), and environmental (model 4) risk factors.



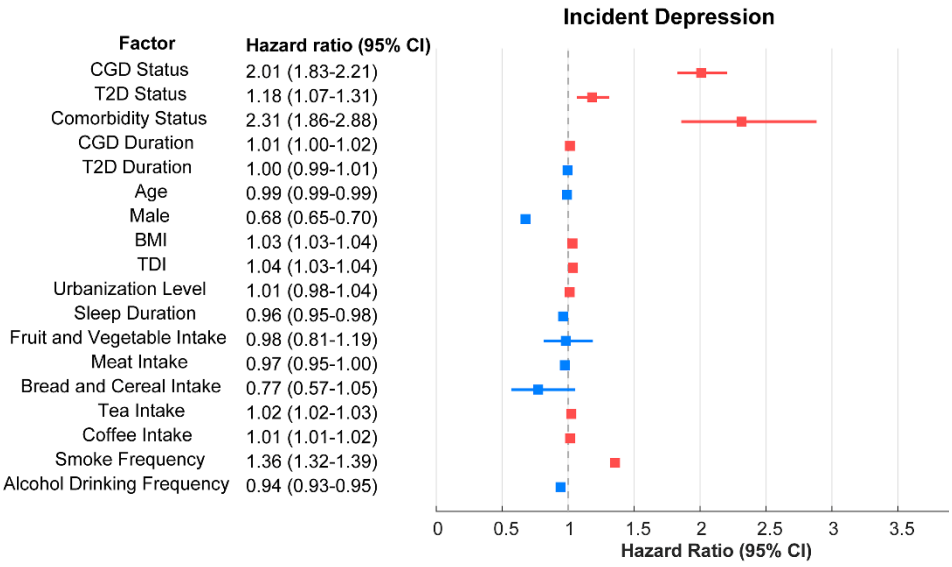
Supplementary Figure 2. Effect of T2D-CGD comorbidity on depression incidence within different follow-up time after adjusting clinical, demographical, environmental, and modifiable lifestyle risk factors.



Supplementary Figure 3. Effect of T2D-CGD comorbidity on incident depression in female and male groups after adjusting clinical, demographical, environmental, and modifiable lifestyle risk factors.



Supplementary Figure 4. Results of sensitive analysis in the scenario where only diagnostic data (ICD-10 code) was used for selecting participants.



Supplementary Figure 5. Results of sensitive analysis in the scenario where subjects who were diagnosed as depressive episodes were included, and those who were only diagnosed as recurrent depressive disorders were excluded.