

Apoptosis protein markers in comorbid type 2 diabetes mellitus and depression; mediators of dementia incidence over 15 years

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Background

- Type 2 diabetes mellitus (T2DM)** and **major depressive disorder** are reciprocal risk factors¹.
- Both T2DM and MDD elevate **dementia risk**².
- T2DM and depression are associated with **apoptosis**, a vital physiological process for which careful homeostatic balance is needed to maintain optimal health³.
- Proteomic markers** of apoptosis have yet to be studied as dementia predictors in T2DM and/or MDD.

Aims

- Determine whether 15-year dementia incidence (Alzheimer’s disease [AD], all-cause dementia [ACD], vascular dementia [VD], frontotemporal dementia [FTD]) differ between the strata of: (i) healthy controls; (ii) depression alone; (iii) T2DM alone; (iv) comorbid T2DM with depression.
- Determine whether the association between apoptosis and 15-year dementia incidence differs between strata.

Methods

Study design: Cross-sectional stratified cohort study of UK Biobank participants.

Participants: Depression was assessed from International Classification of Disease-10th revision (ICD-10) records or physician diagnosis. T2DM was be ascertained as an ICD-10 status, physician diagnosis of T2DM, glycated hemoglobin (HbA1c) >=48mmol/mol, or based on use of an antidiabetic medication.

Protein quantification: Concentrations of plasma proteins were quantified via Olink Explore 3072. KEGG pathway analysis revealed 60 apoptosis-related proteins.

Dementia: Determined over a 15-year follow-up period. Classifications based on electronic health records.

Statistical analysis:

- Cox models estimated dementia risk between strata.
- Interaction terms tested whether strata modified apoptosis protein associations dementia.
- Covariates: age, sex, ethnicity, body mass index, total cholesterol, hypertension, and years of education.
- FDR-correction was applied for multiple comparisons.

Results

Table 1: Participant demographics.

Demographics	Control (n=10,054)	Depression (n=1223)	T2DM (n=3555)	T2DM with depression (n=703)	χ^2
Age (years)	56.3 ± 8.2	55.9 ± 8.1	59.6 ± 7.5	57.7 ± 7.8	477.98
Sex (% female)	5352 (53.2%)	776 (63.5%)	1373 (38.6%)	333 (47.4%)	315.46
Ethnicity (% white)	9506 (94.5%)	1158 (94.7%)	3051 (85.8%)	616 (87.6%)	310.94
BMI (kg/m ²)	27.0 ± 4.4	27.6 ± 5.0	31.1 ± 5.6	31.8 ± 5.9	1957.30
Total cholesterol (mg)	5.7 ± 1.1	5.7 ± 1.2	4.9 ± 1.3	4.9 ± 1.2	1561.0
Hypertension	2616 (26.0%)	427 (34.9%)	2383 (67.0%)	521 (74.1%)	2271.40
Years of education	15.1 ± 5.1	14.8 ± 5.0	13.5 ± 5.4	13.2 ± 5.2	354.55

Kruskal Wallis tests or Chi-square tests were used to detect differences in demographics between the strata. All p<0.05. Continuous variables are reported as mean±SD and categorical variables are reported as N (%).

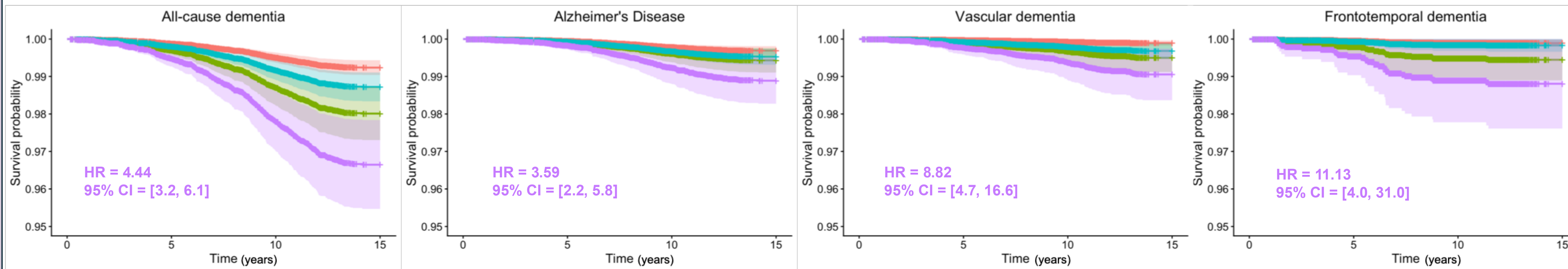


Figure 1: Survival plots of incident ACD, AD, VD, and FTD over 15-years. Adjusted for covariates.

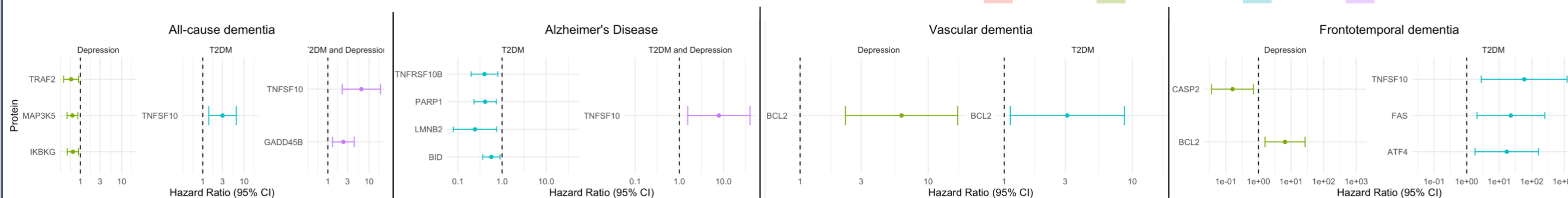


Figure 2: Forest plots representing the interaction between apoptosis proteins and strata predicting ACD, AD, VD, and FTD. Adjusted for covariates and FDR correction. Only significant interactions ($p_{FDR} < 0.05$) are plotted.

Conclusions

Elevated apoptosis markers in blood pinpoint a unique pathophysiological element underlying elevated dementia risk in the context of mood and metabolic comorbidity.

References

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