# Contribution of depression and cardiometabolic diseases and the role of depression treatment in survival and functioning in older adults

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eClinicalMedicine 2025;82: 103182
Published Online xxx
https://doi.org/10.1016/j.eclinm.2025.103182

## Summary

**Background** Achieving survival free from physical disability or neurocognitive impairment, known as disability-free survival (DFS), is a key public health goal. This study aimed to (1) determine the long-term interactive effects of depression and cardiometabolic diseases (CMDs) on DFS, and (2) explore any associated antidepressant treatment effect on improvements in DFS among older adults.

**Methods** We used data from the ASPREE trial and its observational follow-ups (2010–2019), involving community-dwelling adults aged ≥ 70 years (≥65 for U.S. minorities). Time-updated Cox models were used to estimate the combined effect of depression and CMDs (type 2 diabetes, dyslipidemia, hypertension, chronic kidney disease, metabolic-associated steatotic liver disease, and major adverse cardiovascular events) as well as cardiometabolic multimorbidity (≥2 CMDs) on DFS. To evaluate the improvement in DFS associated with antidepressant treatment in individuals with depression, we estimated the number needed to treat (NNT) to achieve a one-year increase in DFS through antidepressant therapy.

**Findings** 18,739 participants (mean [SD] age, 75.1 [4.6] years; 56.0% female) were included, with a median follow-up of seven years; individuals with both depression and CMDs demonstrated a significantly lower DFS compared to those without either condition. In individuals with depressive symptoms, antidepressant use was associated with a median increase in DFS of 2.95 years (95% CI, 2.12–3.04), with an estimated NNT of 8.05 (95% CI, 5.63–14.86) associated with a one-year increase in DFS.

**Interpretation** Integrating depression treatment into chronic disease management, when appropriate, is associated with an improvement in DFS among older adults.

**Funding** Deakin University Postgraduate Research Scholarship.



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Keywords: Depression; Cardiometabolic diseases; Disability-free survival; Antidepressant treatment; Chronic disease management; Healthy aging

## Research in context

### Evidence before this study

Because life expectancy is progressively increasing in many countries, there is a corresponding need to understand how to optimize the quality of aging and promote disability-free survival (DFS), defined as life free from dementia or physical disability. Depression and cardiometabolic diseases (CMDs) are major contributors to morbidity and reduced DFS. We conducted a systematic search of PubMed without language restrictions for articles published from inception to March 2024, using search terms such as "depression", "cardiometabolic diseases", "healthy longevity", "disease-free life expectancy", "disease-free survival", "healthy life expectancy", and "antidepressant treatment". While prior research has established independent associations between depression, CMDs, and adverse health outcomes, the combined association of these conditions on DFS remains underexplored. These studies rely on cross-sectional data, self-reported outcomes, or focus solely on physical disability, limiting their ability to explore causal relationships and comprehensive outcomes like DFS, which includes both neurocognitive and physical components. Notably, we found no prior studies evaluating the potential role of antidepressant therapy in improving DFS, particularly in those with underlying CMDs.

### Added value of this study

This study provides longitudinal evidence on the interactive effects of depression and CMDs on DFS in a large, rigorously characterized cohort of older adults. The findings indicate that both depression and CMDs are significant risk factors for a shortened health span, with depression having a greater impact on lowering DFS than investigated CMDs. Notably, antidepressant therapy emerged as a potential modifiable factor influencing healthspan, as treating an estimated eight individuals with depressive symptoms was associated with a one-year increase in DFS, with a median increase of 2.95 years. To the best of our knowledge, this is the first study to quantify the potential impact of antidepressant therapy on DFS, highlighting the importance of integrating depression management within chronic disease prevention and treatment strategies.

### Implications of all the available evidence

Integrating depression treatment into chronic disease management strategies has the potential to significantly improve DFS in older adults, thereby reducing the burden of dementia and physical disability. Future research should aim to optimize the benefit-risk profile of antidepressants and advance the development of multidisciplinary care models to enhance health span in aging populations.

## Introduction

The world is experiencing a significant demographic transition toward an older population, generally characterized by an increase in life expectancy.[1] However, this increase has not necessarily been paralleled by healthy aging,[1] leading to more individuals living with chronic diseases for extended periods.[2] Cardiometabolic and neuropsychiatric disorders are among the leading contributors to disease burden in older adults, frequently resulting in disability and loss of independence.[3] The societal and economic impacts of such conditions are profound, as they are among the leading concerns for aging populations.[3] Therefore, achieving a life free from dementia and physical disability, known as disability-free survival (DFS), is a major public health goal.[4]

DFS is a composite measure that captures the duration of life spent free from death, dementia, and persistent physical disability, offering a practical and clinically relevant metric for evaluating healthy aging. DFS offers a comprehensive evaluation of aging, considering lifespan, quality of life, and the capacity for independent living. This metric is particularly valuable in studies of older adults, where the primary goal is not merely to prolong life but to extend the healthy, independent years of life.[4]

Cardiometabolic diseases (CMDs), encompassing interrelated conditions that span cardiovascular and metabolic diseases, are among the most prevalent and burdensome chronic conditions in older populations, contributing to significant reductions in life expectancy.[5,6] These conditions contribute significantly to physical disability and long-term neurocognitive impairment through mechanisms such as chronic inflammation, endothelial dysfunction, and metabolic dysregulation.[5] CMDs often co-occur with depression, sharing overlapping pathophysiological pathways such as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neuroinflammation, and lifestyle risk factors.[5,7] These shared mechanisms suggest a potential synergistic effect, where the coexistence of CMDs and depression may amplify the risk of physical disability and neurocognitive impairment.[8,9] In addition, previous studies have shown a dose-response relationship between the increasing number of CMDs and the risk of adverse clinical outcomes, indicating that the concurrent presence of two or more CMDs—referred to as cardiometabolic multimorbidity (CMM)—is associated

with substantial reductions in longevity.[6,10] Notably, evidence suggests an average reduction in life expectancy of approximately 15 years for individuals aged 60 years, with up to 23 years of life lost for those with three cardiometabolic conditions at the age of 40 years.[6]

Although previous research has primarily demonstrated the independent effects of depression and CMDs on functional or cognitive decline, few studies have explored the joint effects of these conditions. Many existing studies have relied on cross-sectional data and self-reported information, which limits the ability to draw causal conclusions and often underestimates the presence of undiagnosed health conditions. Moreover, these studies have typically focused on physical disability, with less emphasis on the impact of these conditions on neurocognitive impairment.

To address these gaps, our study utilizes longitudinal data to investigate the interactive effects of depression and common CMDs on DFS in older adults. Fig. 1 illustrates our conceptual framework, in which co-occurring depression and CMDs are hypothesized to accelerate functional decline and shorten healthy lifespan, and where effective depression treatment may help counteract these adverse effects. Previous studies have primarily focused on type 2 diabetes mellitus (T2DM), cardiovascular diseases, hypertension, and dyslipidemia as CMDs; however, we expanded this definition to include metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic kidney disease (CKD).[5] MASLD, characterized by hepatic steatosis with at least one cardiometabolic criterion, has been associated with a significantly increased risk of persistent physical disability in older adults.[11] Additionally, CKD is a prevalent condition among older populations, contributing to increased mortality and substantial reductions in life expectancy. Beyond evaluating individual CMDs, our study also examines the interactive effects of CMM and depression on DFS. Additionally, we explored the potential benefits of antidepressant treatment in improving DFS among individuals with depressive symptoms, offering insights into targeted therapeutic strategies that may enhance healthy and independent aging.

## Methods

### Study design and participants

The ASPirin in Reducing Events in the Elderly (ASPREE) study was a double-blind, randomized, placebo-controlled trial that revealed no benefit of low-dose aspirin in extending DFS over a median of 4.7 years (IQR, 3.6–5.7).[7] From March 2010 through December 2014, 19,114 community-dwelling subjects from Australia (87.4%) and the United States (12.6%)

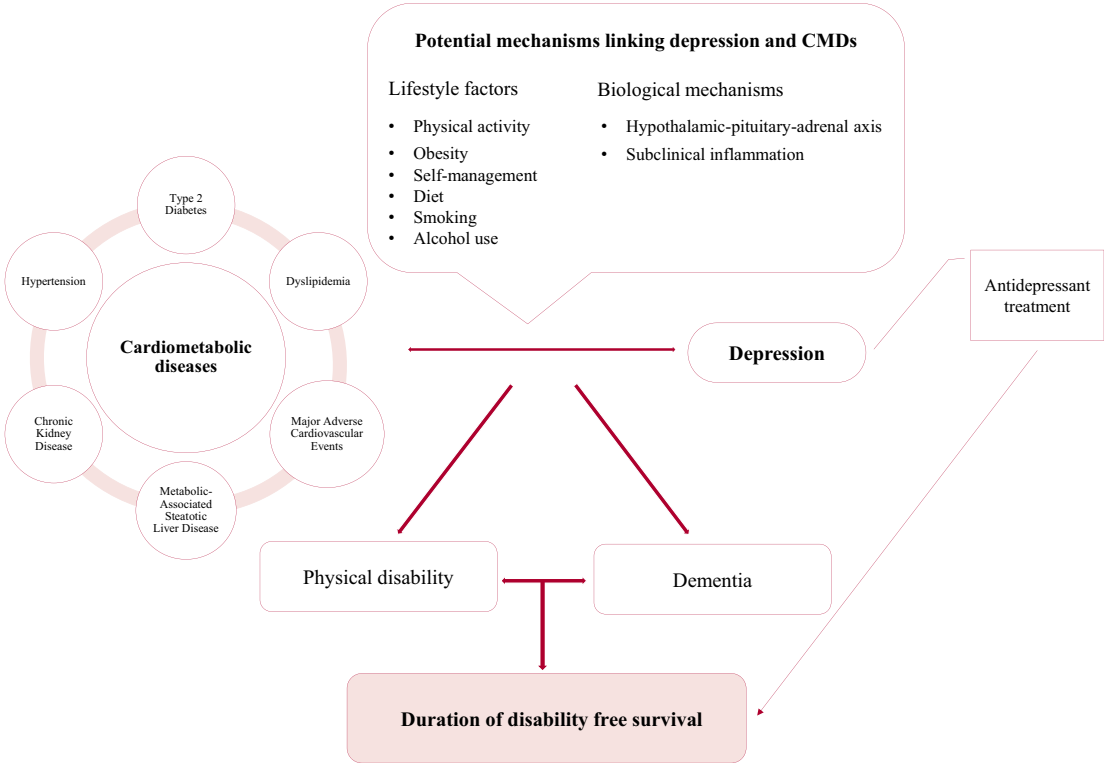


*Fig. 1:* Schematic diagram showing the conceptualization of the study.

who were aged ≥70 years (≥65 for U.S. ethnic minorities), with no prior history of cardiovascular disease, dementia, or major physical disability at trial entry were recruited. The intervention phase ended in June 2017.[7] Of the 17,546 surviving and non-withdrawn participants at the end of the ASPREE trial, 16,317 consented to an additional 5-year follow-up as part of the ASPREE-eXTension study, with no significant differences observed in key demographic or clinical characteristics between those who consented and those who did not.[11] For this analysis, the end of the follow-up was the second ASPREE-XT annual visit (the last visit was completed in August 2019).

### Participant selection

All ASPREE participants were eligible for inclusion in the present study unless they were prescribed any antipsychotic medications at baseline (Supplementary eFig. S1). Participants on such medications were excluded (n = 375) on the basis that (1) antipsychotic use could significantly increase the risk of shortened DFS[12]; and (2) some second-generation antipsychotics are associated with cardiometabolic side effects, including weight gain, lipid disturbance, and glucose dysregulation, which could confound the relationship between depressive symptoms and cardiometabolic outcomes.[13]

### Defining outcomes

The primary outcome, DFS, was defined as survival free of incident dementia or incident persistent physical disability and was the primary prespecified outcome in ASPREE. The primary composite endpoint was derived from the first occurrences of death, dementia, or persistent physical disability. The diagnosis of dementia was adjudicated according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Persistent physical disability was defined as a self-reported inability to perform, severe difficulty in performing or requiring assistance to complete at least one of six basic Activities of Daily Living from the LIFE Disability questionnaire, persisting for at least six months (Details regarding ASPREE primary endpoints are provided in Supplementary appendix).[4]

The secondary outcome of this study was cognitive decline. Cognitive function was assessed using a comprehensive battery of tests, including the Modified Mini-Mental State Examination (3MS) for global cognitive function, the Controlled Oral Word Association Test (COWAT) for phonemic verbal fluency, the Symbol Digit Modalities Test (SDMT) for attention and psychomotor speed, and the delayed recall task from the Hopkins Verbal Learning Test-Revised (HVLT-R) to evaluate episodic memory. Cognitive decline was defined as >1.5 standard deviations (SD) decline in the follow-up cognitive score compared to baseline on any of the four cognitive tests at any follow-up visit (Further information and references can be found in eMethods).

### Defining exposures

a) The definitions for each CMD are provided in eMethods. In this study, T2DM, hypertension, CKD, dyslipidemia, and MASLD were prevalent at baseline, with incident cases added in a time-updating manner. In contrast, major adverse cardiovascular events (MACE) cases emerged as incident events during the follow-up period.
b) Cardiometabolic multimorbidity (CMM) was defined as having two or more from five CMDs including hypertension, dyslipidemia, T2DM, MACE, and CKD. The distribution of the number of comorbid CMDs is presented in Supplementary eFig. S3.
c) Depressive symptoms were obtained annually using the Center for Epidemiologic Studies Depression Scale 10-item (CES-D-10).[14] Depression was assessed as a binary outcome: non-depression (CES-D-10 < 8) and probable depression (CES-D-10 ≥ 8) (Further information and references can be found in eMethods).
d) Antidepressant exposure was defined as any reported use of antidepressant medication at baseline and during follow-up.

### Assessment of potential confounders

The following variables were considered potential confounders: age at baseline, considered as a continuous variable; sex, categorized into male and female; education level, grouped as school year 12 and under and above year 12; ethnicity, distinguishing White from others; smoking status, denoted as smoker and non-smoker; alcohol consumption was assessed by a self-report questionnaire and stratified into abstinence, occasional, moderate, and above-guideline consumption; body mass index (BMI) was calculated by dividing weight (kg) by height squared ($m^2$). For our analysis, smoking status, BMI, and alcohol consumption were treated as time-updating variables, and all other potential confounding variables were considered time-constant, using baseline information.

Baseline cognitive function was evaluated using the sum of z-scores from four cognitive assessments. These included the Controlled Oral Word Association Test for letter F (COWAT), assessing verbal fluency; the Symbol Digit Modalities Test (SDMT), measuring processing speed; the Hopkins Verbal Learning Test-Revised (HVLT-R), evaluating verbal delayed recall; and the Modified Mini-Mental State examination, which assesses a broad spectrum of cognitive functions.[15]

Missing values of covariates were imputed using the single predictive mean matching method, accounting for 4.4% missing data.

### Statistical analysis

Participants were categorized based on the presence of CMDs and depressive symptoms: 1) free from investigated cardiometabolic diseases, no depressive symptoms;

2) presence of investigated cardiometabolic diseases, no depressive symptoms; 3) free from investigated cardiometabolic diseases, presence of depressive symptoms; and 4) presence of investigated cardiometabolic diseases, presence of depressive symptoms. The group without either condition serves as the reference.

Multivariable time-updating Cox proportional hazard models were used to estimate hazard ratios (HRs) of combined depression and CMD on DFS. Depression status and CMDs were included as time-updating covariates, with each CMD added to the model individually to evaluate its specific impact on DFS over the follow-up period. The models were adjusted for age, sex, ethnicity, education level, baseline cognitive function, smoking status, alcohol consumption, and BMI. To mitigate multicollinearity, BMI was excluded from the models for MASLD. In addition, we assessed the joint association of CMM and depression on DFS using participants without CMM or depression as the reference group, employing similar time-updating Cox proportional hazards models. To account for multiple hypothesis testing, p-values were adjusted using the Benjamini-Hochberg procedure, with an estimated false discovery rate (FDR) of 5% ($p < 0.05$) considered statistically significant.

Associated antidepressant use effects on DFS were estimated using model-based median survival difference and the number needed to treat (NNT) (Supplementary eFig. S2). Interaction effects between depression and CMDs were explored using the Synergy Index (SI), Relative Excess Risk due to Interaction (RERI), and Attributable Proportion (AP). Detailed statistical methods are provided in eMethods.

### Sensitivity analysis

To assess the robustness of our findings, we conducted sensitivity analyses to evaluate the potential impact of misclassification of depressive symptoms, we used an alternative CES-D-10 cut-off score of 12 and modeled the total CES-D-10 score as a continuous variable.

### Subgroup analysis

We compared individuals with CMM without depression, individuals with depression without CMD, and individuals with both CMM and depression, with the individuals without CMD and depression as the reference group.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

### Baseline sample characteristics

Among the 18,739 participants with a maximum follow-up of nine years, the mean (SD) age at study entry was 75.1 (4.6) years, 93.5% were White, and 56.0% were female. At baseline, most participants in both the non-depression and probable depression groups were moderate alcohol consumers and non-smokers. The mean (SD) BMI was slightly higher in the probable depression group at 28.7 (5.3) $kg/m^2$ compared to 28.0 (4.6) $kg/m^2$ in the non-depression group (Table 1).

### Impact of CMDs and depression on DFS

Table 2 shows the estimated adjusted HRs and median survival differences for the effects of CMDs and depressive symptoms on DFS. Participants with T2DM without depressive symptoms had a 15.9% lower DFS (median DFS was 3.37 years shorter) compared to those without either condition. Those with both T2DM and depressive symptoms had a 34.6% lower DFS (median DFS was 4.51 years shorter). For dyslipidemia, DFS was 16% lower among participants without depressive symptoms and 28.6% lower among those with both conditions (median DFS were 0.10 and 1.62 years shorter, respectively). Participants with MASLD without depressive symptoms had a 2.9% lower DFS compared to those without MASLD or depressive symptoms, with a median DFS that was 0.73 years shorter. Among participants with both MASLD and depressive symptoms, DFS was 32% lower, with a median DFS that was 2.99 years shorter. CKD showed a similar pattern, participants without depressive symptoms had a 4.8% lower DFS (median DFS was 3.37 years shorter). Among those with both CKD and depressive symptoms, DFS was 25.4% lower, with a median DFS that was 5.37 years shorter. A similar pattern was observed for MACE, DFS was 8.3% lower in the absence of depressive symptoms and 39.4% lower when both MACE and depressive symptoms were present (median DFS were 0.88 and 3.63 years shorter, respectively). For hypertension, the DFS rate was estimated to be a non-significant 3% higher in participants without depressive symptoms and 20.6% lower in those with depressive symptoms (median DFS were 1.07 and 2.49 years shorter, respectively). We also observed that participants with two or more CMDs (CMM) and depressive symptoms had a 36.71% lower DFS rate compared to those with fewer than two CMDs and without depressive symptoms. In addition, the presence of depressive symptoms in older adults free from the investigated CMDs was associated with an approximate 19%–27% lower DFS (Fig. 2), with median DFS being 2.86–3.63 years shorter (Table 2).

Our results showed that across all the investigated CMDs, female sex, higher education level, moderate alcohol consumption, and higher baseline cognitive score were significantly associated with longer DFS duration. In contrast, older age, higher BMI, and smoking history were significantly associated with lower DFS duration. Notably, smoking emerged as the strongest prognostic factor, with a history of smoking significantly reducing DFS (HRs: 1.74–1.85) (Supplementary eTable S2).

| | Non-depression (CES-D-10 Score <8) | Probable depression (CES-D-10 Score ≥ 8) | All participants |
|---|---|---|---|
| Number of participants | 16,930 | 1809 | 18,739 |
| Sex Female (n, %) | 9300 (54.9%) | 1198 (66.2%) | 10,498 (56.0%) |
| Age (y) (mean ± SD) | 75.1 (4.5) | 75.2 (4.7) | 75.1 (4.6) |
| Alcohol consumption (n, %) | | | |
| No history of alcohol consumption | 3810 (22.7%) | 487 (27.3%) | 4297 (23.2%) |
| Occasional drinkers | 4221 (25.2%) | 462 (25.9%) | 4683 (25.2%) |
| Moderate drinkers | 7218 (43.0%) | 705 (39.5%) | 7923 (42.7%) |
| Above-guideline drinkers | 1524 (9.1%) | 132 (7.4%) | 1656 (8.9%) |
| Education level (Above year 12) (n, %) | 9255 (55.2%) | 962 (53.9%) | 10,217 (55.1%) |
| Ethnic background (n, %) | | | |
| Non-White | 1020 (6.1%) | 171 (9.7%) | 1191 (6.5%) |
| White/Caucasian | 15,577 (93.9%) | 1597 (90.3%) | 17,174 (93.5%) |
| Current smokers (n, %) | 597 (3.6%) | 101 (5.7%) | 698 (3.8%) |
| BMI (kg/m$^2$) (mean ± SD) | 28.0 (4.6) | 28.7 (5.3) | 28.1 (4.7) |
| Dyslipidemia (n, %) | | | |
| Baseline occurrence | 6288 (37.5%) | 667 (37.2%) | 6955 (37.5%) |
| Cumulative occurrence | 9112 | 910 | 10,084 |
| Type 2 diabetes mellitus (n, %) | | | |
| Baseline occurrence | 1513 (8.9%) | 211 (11.7%) | 1724 (9.2%) |
| Cumulative occurrence | 3405 | 415 | 3821 |
| MASLD (FLI ≥ 60) (n, %) | | | |
| Baseline occurrence | 2650 (15.7%) | 279 (15.4%) | 2929 (15.6%) |
| Cumulative occurrence | 3433 | 382 | 3816 |
| Hypertension (n, %) | | | |
| Baseline occurrence | 12,952 (76.5%) | 1404 (77.6%) | 14,356 (76.6%) |
| Cumulative occurrence | 15,755 | 1697 | 17,455 |
| MACE (n, %) | | | |
| Baseline occurrence | 0 | 0 | 0 |
| Cumulative occurrence | 993 | 99 | 1092 |
| Chronic kidney disease (n, %) | | | |
| Baseline occurrence | 4262 (25.2%) | 480 (26.5%) | 4742 (25.3%) |
| Cumulative occurrence | 10,943 | 1208 | 12,153 |
| Laboratory values | | | |
| GGT (U/L) (mean ± SD) | | | |
| ALT (U/L) (mean ± SD) | 20.4 (10.5) | 20.1 (14.1) | 20.4 (10.9) |
| AST (U/L) (mean ± SD) | 21.9 (7.4) | 22.0 (9.8) | 21.9 (7.6) |
| Total cholesterol (mg/dl) (mean ± SD) | 202.7 (38) | 202.5 (38.8) | 202.6 (38.1) |
| HDL cholesterol (mg/dl) (mean ± SD) | 61.2 (17.8) | 61.1 (17.3) | 61.2 (17.8) |
| Triglycerides (mg/dl) (mean ± SD) | 116.9 (58.3) | 121.4 (58.2) | 117.3 (58.3) |
| Fasting blood glucose (mmol/L) (mean ± SD) | 5.5 (1.0) | 5.5 (1.2) | 5.5 (1.0) |

CES-D, Center for Epidemiologic Studies Depression; BMI, Body Mass Index; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MACE, major adverse cardiovascular events; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase. Major adverse cardiovascular events (MACE) included CHD death, non-fatal myocardial infarction, and fatal or non-fatal ischemic stroke. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or use of antihypertensive medication. T2DM was defined by self-report, glucose-lowering medication use, or FPG ≥ 126 mg/dL (7.0 mmol/L). Dyslipidemia included cholesterol-lowering medication use, serum total cholesterol ≥212 mg/dL (5.5 mmol/L, Australia) or ≥240 mg/dL (6.2 mmol/L, USA), or LDL > 160 mg/dL (4.1 mmol/L). CKD was defined as eGFR < 60 ml/min/1.73 m$^2$ or spot urine ACR ≥ 3 mg/mmol. MASLD was defined using FLI and meeting at least one cardiometabolic criterion.

***Table 1:*** **Characteristics of study participants.**

RERI and AP values were negative for dyslipidemia, hypertension, and CKD, suggesting antagonistic interactions, with a significant interaction observed for dyslipidemia. For T2DM and MACE, positive RERI and AP values indicate a possible interaction; however, interaction effects were non-significant for T2DM. In contrast, MACE showed a significant synergistic interaction, with a positive AP and an SI value above 1 (Supplementary eTable S1). Antagonistic interactions imply a combined effect less severe than expected, whereas synergistic interactions indicate a greater combined impact on DFS.

A subgroup analysis indicated that participants with both CMM and depressive symptoms had a significantly increased risk of shortened DFS (HR 1.36, 95% CI 1.15–1.60) compared to those without any underlying CMDs and depressive symptoms. A significant lower DFS was also observed among individuals with depression without any underlying CMDs (1.25, 1.01–1.55). Conversely, no significant association was found for individuals with CMM without depression.

### Effect of treatment with antidepressants

In individuals with depressive symptoms, using antidepressants was associated with a 12% increase in DFS. This increase was slightly higher at 14% among individuals with CMDs. In addition, antidepressant use was associated with a 2.95 (2.12–3.04) years increase in DFS across the total sample, and similar patterns were observed in individuals with CMDs (Table 3). The estimated NNT associated with a one-year increase in DFS was 8.05 (5.63–14.86) for the total population, indicating that treating eight individuals is associated with a one-year increase in DFS. Among those with CMDs, the NNTs were slightly lower at 7.39 (Table 3). Comparing the sociodemographic and clinical characteristics of antidepressant users and non-users revealed that antidepressant users were more likely to have greater social support (51.1% vs. 46.1%, $p = 0.021$), experience polypharmacy (62.6% vs. 40.9%, $p < 0.001$), and have a slightly higher mean number of comorbidities (2.6 vs. 2.4, $p < 0.001$), serum triglycerides (126.2 vs. 118.0 mg/dL, $p < 0.001$), and HDL-C (62.6 vs. 61.1, $p = 0.018$) levels. However, no significant differences were observed between the groups in social interactions, social isolation, or other clinical and laboratory measures (Supplementary eTable S3).

Among antidepressant users, amitriptyline was the most frequently prescribed medication over seven annual visits, followed by selective serotonin reuptake inhibitors, primarily sertraline and escitalopram, and atypical antidepressants, mainly mirtazapine (Supplementary eTable S4).

### Impact of CMDs and depression on cognitive decline

The results of our secondary analyses, evaluating cognitive decline as the outcome, were consistent with our primary findings. Participants with both depressive symptoms and CMDs generally showed higher hazard ratios for cognitive decline compared to those without

| | HR (95% CI) | p-value[b] | Median[a] (Years) (95% CI) |
|---|---|---|---|
| **Type 2 diabetes mellitus** | | | |
| No depressive symptoms, no diabetes | 1.00 | <0.001 | 0.00 |
| Diabetes, no depressive symptoms | 1.19 (1.14, 1.24) | | −3.37 (−4.37, −2.37) |
| Depressive symptoms, no diabetes | 1.31 (1.26, 1.36) | | −3.37 (−4.37, −3.07) |
| Diabetes, depressive symptoms | 1.53 (1.43, 1.65) | | −4.51 (−5.37, −3.35) |
| **Dyslipidemia** | | | |
| No depressive symptoms, no dyslipidemia | 1.00 | <0.001 | 0.00 |
| Dyslipidemia, no depressive symptoms | 1.19 (1.15, 1.24) | | −0.10 (−1.13, 0.80) |
| Depressive symptoms, no dyslipidemia | 1.35 (1.30, 1.41) | | −3.13 (−3.59, −2.95) |
| Dyslipidemia, depressive symptoms | 1.40 (1.30, 1.50) | | −1.62 (−2.13, −0.35) |
| **MASLD** | | | |
| No depressive symptoms, no MASLD | 1.00 | <0.001 | 0.00 |
| MASLD, no depressive symptoms | 1.03 (1, 1.07) | | −0.73 (−3.22, −0.52) |
| Depressive symptoms, no MASLD | 1.34 (1.29, 1.38) | | −2.92 (−3.53, −1.82) |
| MASLD, depressive symptoms | 1.47 (1.38, 1.57) | | −2.99 (−4.22, −1.39) |
| **Hypertension** | | | |
| No depressive symptoms, no hypertension | 1.00 | <0.001 | 0.00 |
| Hypertension, no depressive symptoms | 0.97 (0.92, 1.02) | | −1.07 (−1.23, −0.66) |
| Depressive symptoms, no hypertension | 1.38 (1.25, 1.53) | | −2.81 (−4.28, −0.93) |
| Hypertension, depressive symptoms | 1.26 (1.19, 1.33) | | −2.49 (−3.28, −0.83) |
| **Chronic kidney disease** | | | |
| No depressive symptoms, no CKD | 1.00 | <0.001 | 0.00 |
| CKD, no depressive symptoms | 1.05 (1.01, 1.08) | | −3.37 (−3.93, −2.80) |
| Depressive symptoms, no CKD | 1.35 (1.28, 1.42) | | −3.30 (−4.19, −1.82) |
| CKD, depressive symptoms | 1.34 (1.27, 1.41) | | −5.37 (−5.37, −4.37) |
| **MACE** | | | |
| No depressive symptoms, no MACE | 1.00 | <0.001 | 0.00 |
| MACE, no depressive symptoms | 1.09 (1.01, 1.20) | | −0.88 (−2.37, −0.54) |
| Depressive symptoms, no MACE | 1.30 (1.26, 1.35) | | −2.13 (−4.92, −0.87) |
| MACE, depressive symptoms | 1.65 (1.39, 1.95) | | −3.63 (−4.37, −3.35) |
| **CMM[c]** | | | |
| No depressive symptoms, CMD < 2 | 1.00 | <0.001 | 0.00 |
| CMM, no depressive symptoms | 1.02 (0.93, 1.12) | | −0.33 (−0.34, −0.44) |
| Depressive symptoms, CMD < 2 | 1.54 (1.39, 1.70) | | 0.09 (−0.07, 0.05) |
| CMM, depressive symptoms | 1.58 (1.39, 1.79) | | −0.12 (−0.21, −0.22) |

MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MACE, major adverse cardiovascular events; CMD, Cardiometabolic disease, CMM, Cardiometabolic multimorbidity. [a]Reduction in the median disability-free time compared with the median disability-free time for no depression symptoms, no comorbid group. [b]P-values were adjusted for multiple comparisons using the Benjamini–Hochberg method to control the false discovery rate. The adjusted p-value for the included model is 2.00e-16.2. [c]CMM: Cardiometabolic multimorbidity, defined as having two or more CMDs including hypertension, dyslipidemia, type 2 diabetes, MACE, and chronic kidney disease.

***Table 2:*** **Model-adjusted hazard ratios and median disability-free survival for the joint effect of investigated cardiometabolic disorders and depressive symptoms in the total population.**

either condition. Consistent with the primary analysis, the combination of depressive symptoms and MACE was associated with the greatest risk of cognitive decline (Supplementary eFig. S5).

### Power analysis

A post hoc power calculation indicated that the study had sufficient power (>80%) to detect small and moderate HRs in the range of 1.07–1.15.

## Discussion

This large-scale prospective study of community-dwelling older adults provides several key insights into the relationships between depression, common CMDs, and DFS. First, the presence of comorbid depression was consistently and significantly associated with a lower DFS across all examined conditions. Second, the use of antidepressants in older adults with both underlying CMDs and depressive symptoms was significantly associated with an improvement in DFS. Treating seven individuals with depressive symptoms was associated with an estimated one-year increase in DFS, suggesting that depression treatment in targeted populations could be effective in extending DFS after considering the benefit-risk ratio of antidepressant medications.

Depressive symptoms often co-occur with chronic conditions in older adults, exacerbating their progression

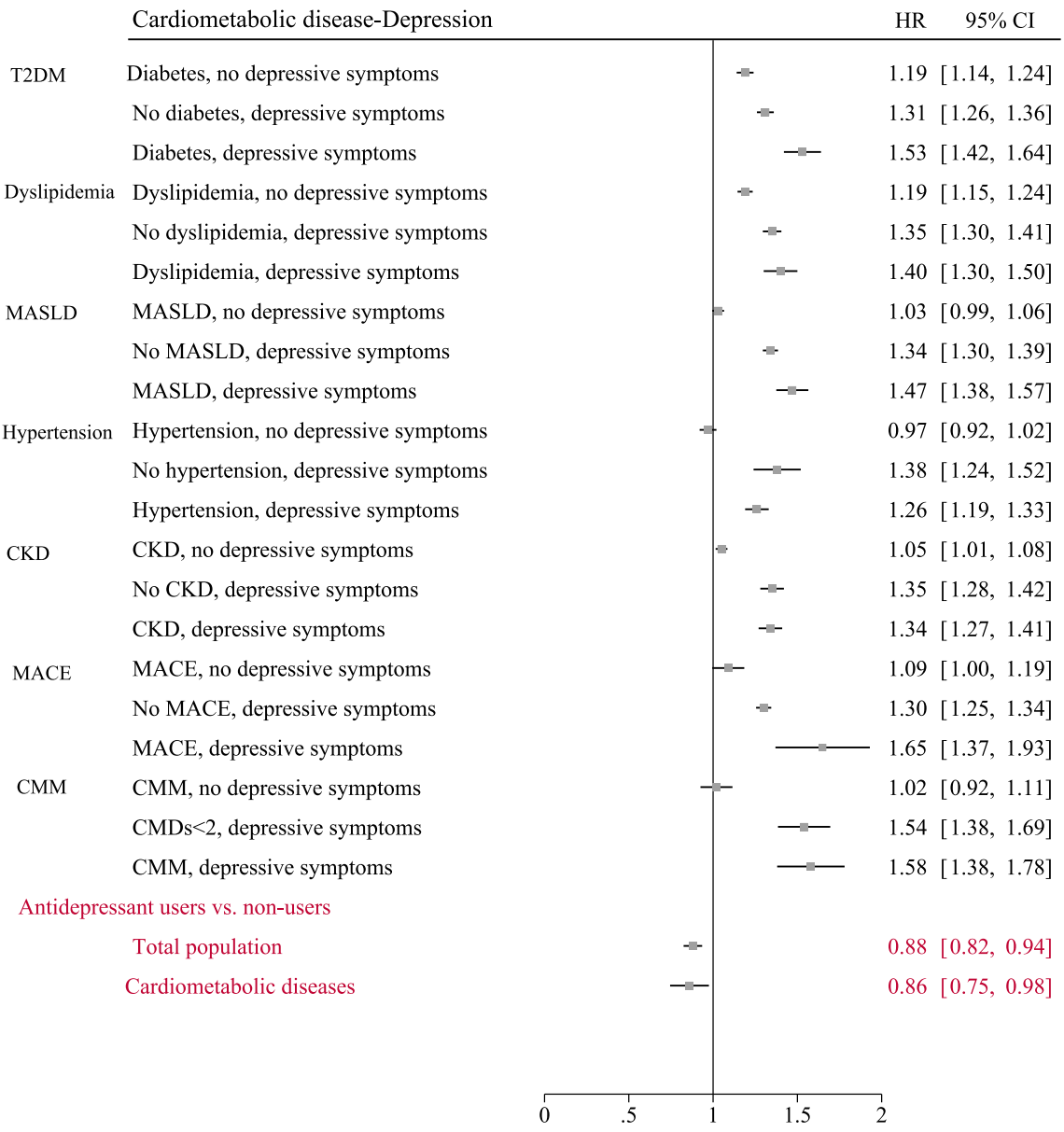


***Fig. 2:*** Adjusted hazard ratios for disability-free survival by depression status and cardiometabolic disease. CMD, Cardiometabolic disease; CMM, Cardiometabolic multimorbidity, MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MACE, major adverse cardiovascular events; CKD, chronic kidney disease; HR, Hazard ratio. CMM: Cardiometabolic multimorbidity, defined as having two or more CMDs including hypertension, dyslipidemia, type 2 diabetes, MACE, and chronic kidney disease.

and increasing the overall burden on health outcomes.[14] Our findings indicate that individuals with both depressive symptoms and CMDs had a significant lower DFS compared to those with either condition alone. Immunometabolic dysregulation, including chronic low-grade inflammation, oxidative stress, and disruptions in neuroendocrine function such as leptin dysregulation and insulin resistance, has been implicated in both CMDs and depression.[7,16] These shared mechanisms may contribute to the pathophysiology of both conditions, exacerbating their coexistence. Depression may contribute to or worsen CMDs through dysregulation of the HPA axis, including elevated cortisol levels, a known risk factor for the development of metabolic syndrome. Elevated cortisol contributes to metabolic disturbances such as glucose intolerance, dyslipidemia, weight gain, and hypertension, aggravating underlying conditions like T2DM, dyslipidemia, CVD, and CKD.[17] Furthermore,

| | Antidepressant users (Person-years) | Antidepressant non-users (Person-years) | HR | 95% CI (HR) | p-value | NNT[a] | 95% CI (NNT) | Median | 95% CI (Median) |
|---|---|---|---|---|---|---|---|---|---|
| Total population | 4215 | 4567 | 0.88 | 0.82–0.93 | 0.0001 | 8.05 | 5.63–14.86 | 2.95 | 2.12–3.04 |
| Cardiometabolic diseases[b] | 905 | 1069 | 0.86 | 0.76–0.99 | 0.025 | 7.39 | 4.09–91.73 | 2.92 | 1.40–4.02 |

[a]The number needed to treat (NNT) was calculated to evaluate the impact of antidepressant treatment on improving disability-free survival by one year among individuals with depressive symptoms (CES-D-10 score ≥8). At baseline, 3537 participants with either depressive symptoms or antidepressant use were included, and they were subsequently categorized based on antidepressant use during the first follow-up. Of these, 2134 participants used antidepressants at the first follow-up, while 1403 were not. Cox proportional hazard models were used to estimate the one-year survival probabilities for antidepressant users and non-users, for those with any cardiometabolic disease. A one-year time lag was applied between depression status, antidepressant use, and cardiometabolic conditions to account for temporal relationships. The absolute risk reduction (ARR) was calculated from the difference in survival probabilities between the treated and untreated groups, and the NNT was obtained as the reciprocal of the ARR. [b]Cardiometabolic diseases including type 2 diabetes mellitus, dyslipidemia, hypertension, major adverse cardiovascular events, and chronic kidney disease.

***Table 3:*** **The estimated 'Number Needed to Treat' for depression treatment by using antidepressants to increase disability-free survival by one year in individuals with depressive symptoms.**

high cortisol levels may worsen MASLD, not only through the components of metabolic syndrome but also by directly increasing the fatty liver index score.[17] CMDs can also worsen depressive symptoms through increased physical limitations, chronic pain, and ongoing medical management demands. The stress of managing a long-term illness, coupled with physical limitations, often triggers or exacerbates depressive symptoms. Biological factors, such as systemic inflammation and neuroendocrine dysregulation, further contribute to the risk of depression in individuals with CMDs.[8] Consequently, individuals with comorbid depression and CMDs show significantly higher rates of functional and mental decline and disability. Theoretically, both depression and comorbid non-communicable medical disorders share both risk factors and pathophysiological pathways. These contribute to the genesis and progression of mental health and medical disorders; processes called neuroprogression and somatoprogression respectively.[18,19] This emphasizes the need for comprehensive, integrated treatment strategies to manage both mental and physical health conditions to optimize long-term survival outcomes.

Both depression and CMDs are significant risk factors for a shortened health span, with depression having a greater impact on lowering DFS than CMDs. The results from a previous study also showed that depression is associated with a substantial reduction in DFS controlling for demographic and health-related factors.[9,15] This significant impact can be attributed to the broad influence of depression on both physiological mechanisms and behavioral patterns. Depression dysregulates physiological systems, including immune function and inflammatory pathways. Pro-inflammatory markers are consistently elevated in the serum and cerebrospinal fluid of individuals with depression, even in the absence of comorbid somatic conditions.[20] Conversely, anti-inflammatory cytokines are observed at lower levels in depressed individuals.[20] These dysregulations have wide-reaching effects, including worsening physical health and contributing to cognitive decline.[9] Depression also impacts motivation, decision-making, and behavior, leading to poorer self-care, lower adherence to treatments, and a higher likelihood of engaging in unhealthy behaviors such as smoking, alcohol use, sedentariness, poor diet, and substance use.[21] These behavioral factors further accelerate the decline in functional health and contribute to the overall reduction in DFS. The psychological burden of depression - manifesting as feelings of isolation, fatigue, and hopelessness - further compounds the reduction in DFS. Furthermore, apathy, a common symptom in nearly 40% of depression cases, may independently contribute to physical disability by impairing older adults' perceptions of their functional capacities, demotivating adaptive and healthy activities like hobbies and exercise, further reducing DFS.[15] As a result, depression has a pervasive and profound impact on DFS, even in individuals who are otherwise physically healthy, highlighting the critical need to address mental health as a key factor in promoting long-term functional outcomes.

We observed antagonistic interactions and non-significant synergistic interactions between depression and most investigated CMDs, except for MACE, on DFS. This suggests that, for most conditions, the combined effect of depression and CMDs on DFS was less than the sum of their individual effects. Several interrelated mechanisms may explain this observation. First, depression and CMDs may share overlapping pathophysiological pathways, such as inflammation and neuroendocrine dysregulation, which may not synergistically exacerbate each other as expected.[16] Second, treatments for CMDs might confer secondary benefits on depression or vice versa, thereby reducing the expected cumulative effect.[22] Additionally, behavioral adaptations and comprehensive care in individuals managing both depression and chronic illnesses could further mitigate their negative impact on DFS.[22] Finally, survivor bias might contribute to underestimating the joint effect, as those who survive with both conditions may possess greater resilience or better management strategies. These factors collectively highlight the need for integrated and nuanced approaches to managing comorbid mental and physical health conditions.

We observed a non-significant increase in DFS among individuals with hypertension and a smaller reduction in DFS for those with both hypertension and depression compared to those with depression alone. These findings may be partly attributed to the common use of antihypertensive medications, including renin-angiotensin-system inhibitors, calcium channel blockers, and beta-blockers, among individuals with hypertension in this population.[23] Previous research has demonstrated that these classes of antihypertensive drugs are associated with decreased rates of depression.[24] As such, these medications, through their anti-inflammatory effects and modulation of stress responses, may help mitigate the adverse impact of depression on DFS in individuals with hypertension.

Among the examined CMDs, the combination of depression and major adverse cardiovascular events imposes a greater burden on health outcomes, with MACE showing a significant synergistic interaction with depression that showed a greater lower DFS than either condition alone. This can be attributed not only to the potentially life-threatening nature of MACE but also to several underlying pathophysiological pathways linking depression and atherosclerotic CVD, wherein each condition exacerbates the other.[25] Depression may worsen CVD through mechanisms such as chronic inflammation, endothelium and platelet dysfunction, dysregulation of the HPA axis, and cardiac autonomic dysfunction, all of which increase the risk of adverse cardiac events, such as myocardial infarction or stroke.[25,26] Conversely, CVD can contribute to the onset or worsening of depression through shared biological pathways, reduced physical function, and psychological stress.[27] Additionally, depression can impair adherence to cardiovascular treatments and healthy lifestyle behaviors, further compounding the risk of poor outcomes.[25]

Our findings highlight the critical need to tackle multi-dimensional age-related comorbidities, which encompass physical conditions like cardiometabolic multimorbidity (CMM) as well as psychological factors such as depression. While evidence remains limited regarding the combined impact of CMM and depression on later-life physical disability and cognitive decline, our study advances this understanding by evaluating long-term changes in these conditions and their clinical outcomes.[5] We found that participants with both CMM and depression had significantly shortened DFS and poorer cognitive performance compared to those without these conditions, highlighting the compounded risk posed by coexisting physical and mental health multimorbidity challenges. These findings are consistent with existing literature, demonstrating that CMM is associated with structural brain changes, including lower hippocampal volume and reduced grey matter volume, which are key contributors to increased dementia risk.[5] Furthermore, the multiplicative mortality risk associated with combinations of CMDs has been shown to substantially reduce life expectancy, emphasizing the role of CMM as a crucial factor contributing to shortened DFS.[6]

Our results suggest that the use of antidepressants may be associated with an increase in DFS, particularly in individuals with CMDs. A median increase in DFS of approximately three years in individuals with depressive symptoms who used antidepressants highlights the potential benefits of integrating mental health care into chronic disease management strategies. However, the most commonly used antidepressant in the study, amitriptyline, is not a current first-line treatment for depression[28] and is commonly prescribed for neuropathic pain and a range of other conditions at low doses.[29] These agents were first-line therapies decades ago, and their use may reflect continued administration following successful depression treatment in the past. Consequently, some of the observed benefits of antidepressant use may be attributable to improvements in pain or other disability-related symptoms rather than solely to alleviation of depressive symptoms. The relatively low NNT to achieve a one-year increase in DFS among those with CMDs suggested that targeted depression interventions in these populations may be effective. Although the observed association could be influenced by health-seeking behavior, in our study, several factors minimize the potential for healthy user bias. First, participants in this study were drawn from an RCT, characterized by being socially engaged and health-conscious. Second, our results revealed that antidepressant users and non-users were nearly similar, or even showed favorable characteristics among non-users, in various aspects including lifestyle, social, and clinical factors as well as key serum biomarkers and comparable availability of blood samples, all of which serve as proxies for health service utilization. Despite this, the benefit-risk ratio of antidepressant use should be carefully assessed, as these medications are associated with potential adverse clinical outcomes in the geriatric population.[30]

The strengths of our study include a large, well-characterized sample of community-dwelling older adults, allowing for robust estimations. The use of a validated depression screening tool and comprehensive physical and laboratory assessments ensured accurate diagnosis of CMDs. Additionally, our study benefits from a longitudinal design with a relatively long follow-up period, which enhances the ability to assess temporal relationships. However, there are some limitations in this study. Although the CES-D-10 is a reliable screening tool, it is not a formal diagnostic instrument for depression and may not fully capture the entire spectrum and severity of the disorder. The selection procedure of the ASPREE trial that excluded individuals with severe diseases or advanced disability may introduce a healthy volunteer bias, potentially limiting the

generalizability of our findings to older adults with more severe conditions. Furthermore, we were unable to account for the duration and severity of CMDs or the potential confounding effects of treatments, which may influence the relationship between CMDs, depression, and DFS. Additionally, as this study is observational in nature, residual confounding may persist despite adjustment for key covariates, limiting our ability to draw causal inferences regarding the relationship between depression, CMDs, and DFS.

This study highlights the significant joint association of depression and CMDs with shortened DFS in older adults, with depression exerting a more pronounced effect than the investigated CMDs. Given the aging global population and the role of depression as a leading cause of disability, targeted depression treatment in high-risk individuals may substantially enhance healthy longevity in older adults.

#### Contributors

Dr Davoodian and A/Prof Mohebbi had full access to and verified the data of the study. A/Prof Mohebbi was the senior author.

ND, MF, MB, RLW, AMT, and MM contributed to the study conceptualization and design. JJM, JR, AMT, and RLW contributed to the data curation and investigation. ND and MM contributed to formal analysis, validation, and visualization. ND and MM contributed to writing the original manuscript draft. ND, MF, MB, DCC, RRH, CMYL, ML, JJM, JAP, KP, GR, JR, AMT, RLW, and MM contributed to reviewing and editing the manuscript.

#### Data sharing statement

The de-identified dataset used for this analysis can be accessible to researchers and students via a request to http://ams.aspree.org. Access will be through a web-based data portal safe haven based at Monash University, Melbourne, VIC, Australia.

#### Declaration of interests

A/Prof Woods reported receiving National Institute of Health (NIH) and National Health and Medical Research Council (NHMRC) funding, which is paid to Monash University. Dr Daniel Clayton-Chubb received partial travel support from Norgine to attend the European Association for the Study of the Liver annual meeting in 2023 and travel support from Novo Nordisk to attend the Metabolic Liver Summit in Madrid in 2023.

#### Acknowledgements

ND is supported by the Deakin University Postgraduate Research scholarship.

MF received a scholarship from Deakin University and is supported by Dr Roth Trisno and family through the Trisno Family PhD Research Scholarship awarded by the RANZCP Foundation.

MB is supported by an NHMRC Leadership 3 Investigator grant (GNT2017131).

ASPREE was supported by U01AG029824 from the National Institute on Aging (NIA) and the National Cancer Institute (NCI) at the National Institutes of Health (NIH), as well as grants 334047 and 1127060 from the National Health and Medical Research Council of Australia (NHMRC), and additional funding from Monash University and the Victorian Cancer Agency. ASPREE-XT is supported by U19AG062682 from NIA and NCI.

The authors would like to thank the ASPREE/ASPREE-XT participants who gave their precious time to participate in ASPREE/ASPREE-XT; registered general practitioners; endorsing organizations; and all members of the ASPREE and ASPREE-XT team.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103182.

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