Do Depressive Symptoms Link Chronic Diseases to Cognition among Older Adults? Evidence from the Health and Retirement Study in the United States

Wentian Lu[a*], Manacy Pai[b], Shaun Scholes[a], Baowen Xue[a]

[a] Research Department of Epidemiology and Public Health, University College London, London, United Kingdom

[b] Department of Sociology, Kent State University, Kent, Ohio, United States of America

[*] Corresponding author. Research Department of Epidemiology and Public Health, 1-19 Torrington Place, London, WC1E 7HB, UK. Email: wentian.lu.14@ucl.ac.uk

HIGHLIGHTS

- The total effects of chronic diseases on cognition are partially mediated through depressive symptoms.
- Depressive symptoms mediated approximately 19%–39% and 23%–54% of the total effects of chronic diseases on cognition in men and women, respectively.
- For chronic conditions, which do not contribute to direct damage in brain functions, the psychological pathway could play an important role in contributing to cognitive decline.
- The association between chronic disease and cognition could be a biopsychosocial phenomenon.

ABSTRACT

Background

Few studies have assessed psychological pathways that connect the association between non-psychotropic chronic disease and cognition. We assessed the extent to which the association between the two was mediated by depressive symptoms in older adults.

Methods

Data came from waves 10-13 (2010-2016) of the Health and Retirement Study in the United States (7,651 men and 10,248 women). Multilevel path analysis, allowing for random intercepts and slopes, was employed to estimate the extent to which depressive symptoms mediated the total effect of a chronic disease on cognition.

Results

We found that the presence of stroke, high blood pressure, diabetes, heart problems, and comorbidity, in both men and women, and lung disease in women, was associated with lower levels of cognition. The total effects of chronic diseases on cognition were partially mediated through depressive symptoms. Depressive symptoms mediated approximately 19%–39% and 23%–54% of the total effects of chronic diseases on cognition in men and women, respectively.

Limitations

We relied on self-reported diagnoses of diseases and depressive symptoms. Our use of a multilevel path analysis with random slopes precluded the inclusion of binary/categorical dependent variables, and the estimation of standardized beta values.

Conclusions

To understand the cognitive challenges that chronically ill older adults face, practitioners and policymakers should consider not just the direct symptoms related to chronic diseases, but also the often overlooked psychological conditions faced by older adults.

Key words: psychological condition, chronic condition, cognitive aging, depression

INTRODUCTION

Chronic cardiovascular related conditions including hypertension, diabetes, stroke, obesity, and coronary artery disease have been identified as risk factors for dementia (Korczyn and Halperin 2009; Barnes and Yaffe 2011). Extant work shows that the presence of these chronic diseases is associated with lower levels of cognition (Yohannes et al. 2017; Levine et al. 2015; Gregg et al. 2000; Taylor et al. 2019). The cardiovascular disease (CVD) related pathologic alterations in brain structure may influence cognition (Langa, Foster, and Larson 2004; Leto and Feola 2014; Biessels et al. 2006; Dodd 2015).

Chronic diseases, however, not only can affect cognition through biological mechanisms, but may also influence it indirectly via psychological pathways. Previous studies have suggested that having chronic diseases was associated with a higher risk of depression (Chapman, Perry, and Strine 2005; Luo, Chui, and Li 2020). Chronic illness can alter the course of one's life by bringing about changes in social roles and responsibilities, and reduced physical mobility impacting social activities and interactions. Changes of this nature can undermine one's sense of self and security resulting in despair and depression (Luo, Chui, and Li 2020; Alpass and Neville 2003). Depression has also been identified as a risk factor for dementia (Korczyn and Halperin 2009; Ownby et al. 2006; Barnes et al. 2012). For example, a retrospective cohort study in US adults found that compared with those who had no depressive symptoms in either mid-life (1964–1973) or late-life (1994–2000), the hazard of dementia (2003–2009) increased by approximately 20% for those with mid-life depressive symptoms only, 70% for those with late-life symptoms only, and 80% for those with both (Barnes et al. 2012). The *scarring hypothesis* suggests that onset or episodes of depression render an individual susceptible to cognitive deficits. The cognitive deficits observed in depressed individuals result from enduring changes in both, the physiological and neurochemical components of the body, which emerge around the time of the onset of

depression and cognitive impairment from that point forward (Schaefer et al. 2017). While not discounting the biological mechanisms that directly connect chronic illness to cognition, we posit that depression plays a crucial part by mediating the cognitive health impact of chronic diseases.

To our knowledge, despite the well-established pathophysiological association between cardiovascular health and cognition, no study has investigated the psychological mechanism that potentially lies on the causal pathway from chronic diseases to cognition. Additionally, the associations of other common chronic diseases, such as cancer and arthritis, with cognition, still remain under assessed. Compared to CVD, these chronic diseases may have smaller impacts on brain function (Socal and Trujillo 2018), they may, nevertheless, influence cognition through psychological pathways.

The association between chronic diseases, depression, and cognition may also vary by gender. In previous studies, women had a higher risk of diabetic complications than men, including myocardial infarction and coronary heart disease, both of which are risk factors for dementia (Kautzky-Willer, Harreiter, and Pacini 2016; Nebel et al. 2018). Older women had more chronic conditions than their male peers; and, older women reported more mental distress than their male peers (Carayanni et al. 2012). A case-control study also found that female patients with first-diagnosed, drug-naïve depression reported severer cognitive impairments in visuospatial and constructional categories than male patients (Wang et al. 2020). New research, therefore, is needed to understand the extent to which the relationship between chronic disease and later-life cognition through the pathway of depression is conditioned by gender.

To that end, we drew on longitudinal data from the US Health and Retirement Study (HRS) (Sonnega et al. 2014) to examine whether the associations between non-psychotropic

chronic diseases and age-related changes in cognition among older men and women were mediated by depressive symptoms.

METHODS

Data

Data came from the HRS (Sonnega et al. 2014). HRS is a longitudinal panel study of a representative sample of US adults aged ≥50 years since 1992 (response rate 81.6%). A mixed mode design (in person and by telephone) has been carried out every two years. HRS participants provided informed consent, and the HRS has been approved by the University of Michigan Institutional Review Board and the National Institute on Aging. HRS added six sub-cohorts before and in 2016. We used data from waves 10–13 (2010–2016) in order to include the majority of sub-cohorts. Figure 1 illustrates the procedure of sample selection. Our final sample included 7,651 men and 10,248 women.

Self-reported diagnosed chronic diseases

Participants were asked at each wave whether a doctor had ever told them that they had a stroke, high blood pressure, diabetes, lung disease (such as chronic bronchitis or emphysema), heart problems (including heart attack, coronary heart disease, angina, congestive heart failure, and other heart problems), cancer or arthritis (yes/no). We also summed the total number of reported chronic diseases for each participant to account for disease comorbidity. Time-varying variables of chronic diseases were used for statistical analysis.

Cognition

Cognition was assessed at each wave using a 27-point score (0–27), which was developed based on the HRS data (Crimmins et al. 2011). This composite measure included tests of the immediate word recall (verbal memory: asking respondents to listen to a list of 10 nouns and then repeat them; 0–10) and delayed word recall (verbal memory: respondents

repeated nouns five minutes later; 0–10), the serial 7s (working memory: subtracting 7 from 100 and continue subtracting each subsequent number for five trials; 0–5), and backward counting (attention and working memory: counting backwards for 10 continuous numbers beginning with 20; 0–2). Higher scores indicate better cognition. Individuals with score <7 were identified as having dementia (Crimmins et al. 2011). Time-varying scores were used to permit modelling of change in cognition over the follow-up period.

Depressive symptoms

Depressive symptoms were measured using a modified version of the Center for Epidemiological Studies-Depression (CES-D) scale (8-item scale with yes/no response format, 0–8) and used as a continuous time-varying covariate (Mojtabai and Olfson 2004).

Confounders

Based on previous evidence (Yohannes et al. 2017; Levine et al. 2015; Gregg et al. 2000; Taylor et al. 2019; Maurer 2010), baseline variables (at wave 10) including marital status, ethnicity, education, income (deciles), labor force status, height (meters), self-reported health in childhood, father's education, mother's education, smoking, days of alcohol consumption per week (days), and vigorous physical activity, as well as time-varying age (years), were considered as confounders. See Table 1 for the categories and the reference group for each categorical/binary variable.

Conceptual framework

Figure 2 presents a conceptual framework adapted from previous studies (Socal and Trujillo 2018; Maurer 2010), showing the postulated determinants of later-life cognition and the roles of chronic diseases and depression. In our analysis, chronic disease was an exogenous independent variable, and cognition was the endogenous outcome. Depression was a potential mediator on the pathway from chronic disease to cognition. The total effect of each chronic disease on cognition in later-life was, therefore, separated into direct effect and

indirect effects through depression. Sociodemographic characteristics (e.g., gender, age, ethnicity), early-life health (e.g., self-rated health in childhood, height) and socioeconomic conditions (e.g., parental education), and mid- and later-life conditions (i.e., marital status, labor force status, and behavioral and socioeconomic factors) had postulated confounding effect on the associations between chronic diseases, cognition, and depression.

Statistical analysis

Multilevel path analysis (Muthén and Asparouhov 2009; Muthén, Asparouhov, and Hamaker 2017), allowing for random intercepts (by participant) and slopes (by age), was applied to estimate the proposed conceptual framework (Figure 2). Path analysis estimated the extent to which the introduction of a mediator (i.e., depressive symptoms) mediated the total effect of chronic disease on cognition. This approach models explanatory relationships between outcome variables and covariates, as well as between covariates (Raykov and Marcoulides 2000). In contrast to traditional path analysis, which does not consider the role of time explicitly, our path analysis was conducted in a dynamic way as we used time-varying cognition, chronic diseases and depressive symptoms (Fosen et al. 2006).

We provided an example to explain the multilevel path analysis from stroke to cognition via depressive symptoms (Supplementary Figure S1). At the within-level (cognitive aging), the intercept represented the predicted value (cognitive score) when age was 50. Each individual had their own intercept (score at baseline) and slope (rate of change in cognition), expressed as random effects at the between-level. Each participant's cognitive trajectory was modelled as a function of age and stroke. The age-specific residual term or random error for each individual was assumed to be normally distributed with zero mean. At the between-level, linear regression was applied to examine the association between each chronic disease and depressive symptoms (coefficient: ß$_1$), between depressive symptoms and

cognition (coefficient: $ß_2$), as well as between each chronic disease and cognition (coefficient: $ß_3$) within and across waves (Muthén 1984).

Direct, indirect and total effects were calculated with 95% confidence intervals (CIs). Direct effects represent the effect of each chronic disease on cognition that did not operate through depressive symptoms (i.e., $ß_3$); indirect effects represent the effects of each chronic disease on cognition that operate through depressive symptoms (i.e., $ß_1 x\ ß_2$); the total effect was the sum of the relevant direct and indirect effects (i.e., $ß_3 + ß_1 \times ß_2$) (Raykov and Marcoulides 2000). Only unstandardized regression coefficients were available for multilevel path analysis with random slopes; this can be interpreted as the estimated average absolute change in cognitive score for a one-unit change in an independent variable (versus the reference; e.g., having versus not having a chronic). The percentages of total effects mediated by depressive symptoms (calculated by the ratio of indirect to total effect) were calculated when total effects were statistically significant (P-value <0.05).

For each chronic disease, we first ran a basic model controlling for age only to estimate the total effect of each chronic disease on cognition. In these basic models, we tested the interaction between gender (reference: men) and each chronic disease (reference: no disease). We found that the interactions between gender and high blood pressure (b = -0.71, SE = 0.22), heart problems (b = -0.62, SE = 0.28) and diabetes (b = -0.60, SE = 0.26) were statistically significant and negative in sign. Thus, we stratified all our analyses by gender. Secondly, we ran multilevel path analysis (full model) by including the mediator (i.e., depressive symptoms) and the confounders described above. In a separate analysis, we examined the association between disease comorbidity and cognition through the pathway of depressive symptoms.

Sensitivity analysis

Depression and chronic diseases could be interdependent and co-occur (World Health Organization 2014). Moreover, the *cognitive reserve hypothesis* suggests that individuals with high intelligence in early life are less likely to develop depression in later life (Schaefer et al. 2017). Thus, reverse causation might exist in the relationships between chronic diseases and depressive symptoms, and between depressive symptoms and cognition. We conducted sensitivity analysis using the Cross-Lagged model (Allison 2017) to evaluate the reverse causation in men and women. Standardized estimates with standard errors were calculated to make results comparable across models. The Cross-Lagged model allows for the tests of reciprocal causation and the inclusion of a lagged dependent variable to control for past characteristics of an individual. For example, in one model for stroke, depressive symptoms at wave t was regressed on stroke and depressive symptoms at wave t-1; stroke at wave t was regressed on depressive symptoms and stroke at wave t-1; cognition at wave t was regressed on depressive symptoms and cognition at wave t-1; depressive symptoms at wave t was regressed on cognition and depressive symptoms at wave t-1. Each regression was fully adjusted for other confounders; and, the correlations between stroke and depressive symptoms, and between depressive symptoms and cognition at the same wave were also considered.

Furthermore, to examine the robustness of our main findings, we calculated mediation effects using a different approach. We dichotomized the CES-D score using the cut-off of ≥4 (as having high-risk depressive symptoms) to assess the clinically-relevant depressive symptoms (Mojtabai and Olfson 2004), and re-categorized the composite score of cognition using the cut-offs of <7 (as having dementia) and 7–11 (as having cognitive impairment) (Crimmins et al. 2011). We then generated binary variables for high-risk depressive symptoms (yes/no) and dementia/cognitive impairment (yes/no). Multilevel logistic

regression with random intercepts and slopes was applied to examine the associations between each chronic disease and high-risk depressive symptoms (for indirect effect), between high-risk depressive symptoms and cognitive impairment or dementia (for indirect effect), as well as between each chronic disease and cognitive impairment or dementia (for direct effect). We controlled all of the conceptually relevant confounders in each of our regression models. Therefore, in this new analysis, the mediator and outcome variables outlined in our main analysis were replaced with binary indicators.

Missing data

The full information maximum likelihood (FIML) estimation method (Larsen 2011) was applied to deal with the item non-response for chronic diseases, cognition and other covariates, under the assumptions of missingness at random (when sources of missing data are observed and are included in the model) and multivariate normality. Supplementary Table S1 shows the percentage of missingness by gender in each variable at each wave. The FIML approach estimates a likelihood function for each case, using only the variables that are observed for that case. All available data were used for parameter estimation, and the likelihood functions were accumulated and maximized across the entire sample.

All analyses were performed using Mplus 7.4 (Muthén and Muthén 1998-2011).

RESULTS

Table 1 shows baseline sample characteristics by gender. Men and women had the same mean age. Compared to men, women had higher mean scores of cognition and depressive symptoms, but lower mean height. Median income was higher in men than women. The median number of chronic diseases was two in both, men and women. More than 50% of men and women had high blood pressure. The proportions of stroke, high blood pressure, diabetes and heart problems were greater among men than women, while the proportions of lung disease and cancer were greater among women than men. Arthritis was

prevalent among both genders, but it was distinctly higher among women (59.3%) than men (45.0%). Compared to men, women were less likely to be highly educated, employed and married/partnered, engage in vigorous physical activity, and have highly educated parents and good childhood health. While larger proportions of current smokers and frequent alcohol consumers were found in men than women.

Table 2 (men) and Table 3 (women) present unstandardized regression coefficients with 95%CIs in basic and full models, for the total, direct and indirect effects of chronic diseases on cognition (between-level only; see Supplementary Table S2 and Table S3 for the estimates of the random effects at within-level in basic and full models).

Total effects of chronic diseases

In basic models (i.e., controlling for age only), for both men and women, each chronic disease was associated with lower cognition, except for cancer. For example, compared with those not having had a stroke, having had a stroke was associated with a 2.32-unit (95%CI: 1.58, 3.06) and a 2.67-unit (95%CI: 1.99, 3.35) lower cognitive score on average among men and women, respectively. After adjusting for potential confounders and including depressive symptoms as the mediator (full models), for participants with stroke compared to those without stroke, the total effect of stroke on cognition was reduced to a 1.00-unit (95%CI: 0.29, 1.71) and 1.13-unit (95%CI: 0.35, 1.92) lower cognitive score among men and women, respectively. Similarly, in full models, for both men and women, high blood pressure, diabetes, and heart problems were associated with lower cognition. Lung disease was associated with lower cognition among women only (-0.62; 95%CI: -1.13, -0.11). However, regardless of gender, neither arthritis nor cancer was associated with lower cognition.

Indirect effects of chronic diseases through the mediating pathway of depressive symptoms

In the full model, for all chronic diseases with significant total effects on cognition among both genders, their indirect effects on levels of cognition through pathways via

depressive symptoms were negative in sign. The presence of these chronic diseases was associated with higher depressive scores, which in turn, was associated with lower levels of cognition.

Figure 3 illustrated the pathways via depressive symptoms. Only statistically significant pathways and only between-level variation were shown. Estimates shown in this figure were regression coefficients $ß_1$, $ß_2$ (for indirect effect) and $ß_3$ (for direct effect) with standard errors. The estimates of the indirect effects shown in Table 2 and Table 3 are equal to the product of the two indirect coefficients (i.e., $ß_1 x ß_2$) displayed in Figure 3.

For indirect effects, in general, the presence of chronic disease was associated with higher depression; in turn, a higher depression score was related to a lower cognitive score. For example, in men, having had diabetes was associated with a 0.33-unit (S.E.=0.15) higher CES-D depression score; and a one-unit higher depression score was related to a 0.44-unit (S.E.=0.06) lower cognitive score.

Based on the ratio of indirect to total effects, depressive symptoms mediated approximately 19%–39% and 23%–54% of the total effects of chronic diseases on cognition in men and women, respectively. Depressive symptoms mediated approximately 54% of the total effect of lung disease on cognition in women.

Total number of chronic diseases

In both basic and full models in Table 2 and Table 3, disease comorbidity (measured by the total number of reported chronic diseases) was associated with lower cognition in both genders. Disease comorbidity was also associated with lower cognition through pathways via depressive symptoms. Based on the ratio of indirect to total effects, depressive symptoms mediated approximately 42% and 50% of the total effect of disease comorbidity on cognition in men and women, respectively (Figure 3).

Sensitivity analysis

Table S4 shows the standardized estimates for the relationships between chronic disease in one wave and depressive symptoms in the next wave, and between depressive symptoms in one wave and cognition in the next wave. Table S5 shows the standardized estimates for the relationships between depressive symptoms in one wave and chronic disease in the next wave, and between cognition in one wave and depressive symptoms in the next wave (for reverse causation). In either men or women, more significant relationships were found in Table S4 than Table S5; and in these significant relationships, the values of the standardized estimates were distinctly larger in Table S4 than Table S5, suggesting stronger effects of chronic diseases on depressive symptoms and depressive symptoms on cognition; and so we conclude that the bias caused by reverse causation had a small influence on the main findings.

Table S6 shows the direct and indirect effects of chronic diseases on the binary outcome of dementia/cognitive impairment. Stroke, high blood pressure, diabetes, heart problems, and the disease comorbidity in both men and women, as well as lung disease in women, were associated with higher odds of dementia/cognitive impairment (with both significant direct and indirect effects). These associations were partially mediated through high-risk depressive symptoms (the binary mediator). Based on the ratio of indirect to total effects, high-risk depressive symptoms mediated approximately 17%–44% and 21%–71% of the total effects of chronic diseases on dementia/cognitive impairment in men and women, respectively. Most of these results remain comparable to our main analysis using multilevel path analysis with continuous variables. The mediation effect of high-risk depressive symptoms for the relationship between lung disease and dementia/cognitive impairment in women was larger than that in our main analysis (71% versus 54%). A discussion on

comparing the results between these additional models and our original models can be found under supplementary Table S6.

DISCUSSION

In summary, stroke, high blood pressure, diabetes, heart problems, and the disease comorbidity in both men and women, as well as lung disease in women, were associated with lower cognition. These associations were partially mediated through depressive symptoms; nearly half of these associations were explained by higher depressive symptoms among those with these chronic diseases.

Studies in the US (Wei et al. 2020), Netherlands (Comijs et al. 2009) and four Latin American countries (Socal and Trujillo 2018) also have found significant associations of cardiovascular-related diseases and the accumulation of chronic diseases with different domains of cognition. Findings on the associations of cancer and arthritis with cognition have been mixed. The Latin American study reported statistically significant but weak associations of cancer and arthritis on cognition (Socal and Trujillo 2018). The Dutch study found faster decline in immediate memory among participants with cancer than those without cancer, but also revealed cancer to be positively associated with delayed recall memory, which may be due to survival selection bias (Comijs et al. 2009).

Psychological pathway

We found that depressive symptoms partially mediated the total effects of stroke, heart problems and cardiovascular risk factors on cognition in both genders; and nearly half of these associations were explained by higher depressive symptoms in individuals with these diseases, suggesting the efficacy of the psychological pathway in linking chronic diseases to later-life cognition. The consequences of chronic diseases including symptom burden, functional impairment, and poor quality of life, as well as biological responses in the brain due to changes in visceral afferent neural input or humoral factors released during states of

cardiovascular pathophysiology, can contribute to progression of depressive, anxiety, and other mood disorders (Katon 2003; Grippo and Johnson 2009). Moreover, chronic diseases, which often are accompanied by changes in social roles and responsibilities and receding social networks due to limitations of chronic diseases such as fatigue and a lack of energy, as well as complicated and time-consuming medication and treatments, can result in increased mental distress (Katon 2003; Grippo and Johnson 2009). A systematic review on psychological distress experienced by patients with chronic diseases found that depression was apparent after being diagnosed with chronic conditions, such as diabetes, stroke, heart problems or lung disease. However, overall findings also reveal that over time, improvements in health and functional abilities lead to reduction in mental distress, namely depressive symptoms (DeJean et al. 2013).

Mental distress resulting from chronic diseases, in turn, could accelerate brain changes leading to cognitive decline and dementia through two mechanisms: vascular alterations in the brain, mainly in the form of leukoaraiosis; and, excessive release of corticosteroids, which damage the hippocampus – the region of the brain that primarily is responsible for regulation of learning and memory (Korczyn and Halperin 2009). In the review on geriatric depression and cognitive impairment, researchers found that compared to older adults without depression, depressed older adults reported worse performance on a multitude of cognitive measures including information processing speed, executive functions, and episodic memory (Steffens and Potter 2008). Deficits in information processing speed and executive functions appeared to increase with the severity of depression symptoms, particularly apathy; and executive dysfunction became more common than other domains of cognitive functioning after the first onset of depression occurred in later life (Steffens and Potter 2008).

We also found that compared to stroke which leads to direct damage in brain functions, the mediation effect of depressive symptoms in the association between other chronic conditions and cognition was stronger (e.g., 19% and 23% for stroke versus 39% and 44% for heart problems in men and women, respectively), indicating that for chronic conditions which do not contribute to direct damage in brain functions, the psychological pathway could play an important role in contributing to cognitive decline (Korczyn and Halperin 2009; Katon 2003; Grippo and Johnson 2009).

All these findings suggested that the association between a chronic disease and cognition could be a biopsychosocial phenomenon.

Gender differences in mediation effects

Compared to men, women are more likely to report internalizing symptoms of mental distress, including depression and anxiety. Men, instead, report more externalizing symptoms, such as substance use and aggressive emotions (e.g., anger) (Rosenfield and Smith 2010). Compared to women, men also are more reluctant in reporting mental distress (Simon and Nath 2004). Gender differences also exist in terms of coping, with women relying on emotion-focused coping that includes ruminating whereas men employ problem-focused strategies (Nolen-Hoeksema, Larson, and Grayson 1999). Lastly, the stress-exposure argument (Pearlin 1999) posits that compared to men, women face a greater number of stressors over the life course (e.g., poverty, discrimination, physical and sexual victimization), which could only exacerbate the already stressful experience of chronic illness. The results from our main analysis showed that depressive symptoms mediated approximately 19%–39% and 23%–54% of the total effects of chronic diseases on cognition in men and women, respectively. It seemed that the mediation effect of depressive symptoms was larger in older women than their older male counterparts when having chronic diseases such as heart problems, lung disease, or comorbidity. However, it is not clear whether the

gender differences shown in our present study are clinically meaningful. More research is therefore needed to claim more definitively the extent to which the mediation effect of psychological conditions on the link between chronic disease and cognition varies differentially across gender.

Strengths and limitations

Our study has several limitations. Firstly, we relied on self-reported diagnosed diseases and measure of depressive symptoms. Recall bias in onset of diseases could exist. However, the CES-D scale is capable of distinguishing the severity of depression and providing valid information on which to base decisions about psychiatric treatment (Radloff 1977).

Secondly, a multilevel path analysis with random slopes has limits, including not allowing for the inclusion of binary/categorical dependent variables, and the inability to calculate standardized beta values since the variance of the dependent variables vary over observations. Thus in our multilevel path analysis we could not dichotomize the CES-D score using the well-established cut-off of ≥4 (as having high-level depressive symptoms) to assess the clinically-relevant depressive symptoms (Mojtabai and Olfson 2004), or re-categorize the composite score of cognition using the cut-offs of <7 (as having dementia) and 7–11 (as having cognitive impairment) (Crimmins et al. 2011). Reassuringly, in the sensitivity analysis in which we used binary variables for high-risk depressive symptoms and dementia/cognitive impairment, most of the results (supplementary Table S6) remain comparable to our original results.

Thirdly, the causal directionality between depression and cognition or between chronic conditions and depression continues to be a matter of on-going debate. However, our sensitivity analysis suggested a small influence of the reverse causation on our main findings. Moreover, a systematic review and meta-analysis of longitudinal datasets among 121,749

participants (Scult et al. 2017), as well as a recent work based on the rat model to study the causation between cognitive impairment and depression (Maramis, Mahajudin, and Khotib 2020) suggested that although cognitive impairment could occur before depression, the association between lower cognitive function and subsequent depression was confounded by the presence of contemporaneous depression symptoms at the time of cognitive assessment. As such, cognitive deficits predicting depression likely represent previously deleterious effects of subclinical depressive symptoms on later depressive performance rather than a premorbid risk factor for later depressive disorders.

Notwithstanding these limitations, to our knowledge, our study is the first to explore the psychological mechanism, depressive symptoms, connecting chronic diseases to cognition among older adults. Additionally, our use of the advanced statistical method – multilevel path analysis, allowed for unequal time spacing, and the inclusion of time-varying covariates that are either continuous or discrete measures. Including time-varying cognition allows the associations between these covariates and cognition to vary over time. Sample clustering within individuals is also considered, allowing for variations in pathway between individuals (Muthén, Asparouhov, and Hamaker 2017; Muthén and Asparouhov 2009).

Practice and policy implications

Our study provides empirical evidence on the psychological pathway from chronic diseases to cognition, suggesting that implementing psychological assessment and intervention among older adults with chronic diseases, is still much in need. Older adults with chronic diseases may be reluctant to acknowledge depression as a separate condition or not recognize the distinctness of depression from other chronic diseases given the often overlapping physical symptoms between the two. Screening for and treating depression earlier among older adults may reduce distress and improve symptoms of chronic diseases, leading to better cognitive functioning and quality of life in later life (DeJean et al. 2013).

More and more people are aging “with” disability and not just aging “into” it. So, a sizeable portion of research and policy effort may be better focused on understanding the extent to which psychological trajectories of chronic diseases vary across life course. Our finding also reflects the potential gender disparities in psychological health. As such, to understand the cognitive challenges that chronically ill older adults face requires that practitioners and policymakers consider not just the direct symptoms related to the chronic disease but also the often and otherwise overlooked psychological conditions faced by older adults.

Conclusion

Findings from our study contribute to the literature by highlighting the psychological pathway connecting chronic diseases to later-life cognitive decline. Nearly half of the association could be explained by higher depressive symptoms among older adults with chronic diseases.

Conflict of Interest

None.

Acknowledgements

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Contributors

WL, BX and MP designed the study. WL performed the statistical analysis and wrote the first draft of the manuscript. MP contributed to the writing and revising of the manuscript. BX and SS assisted WL with refining the analysis and interpreting results. All authors provided critical feedback on the multiple drafts of the manuscript.

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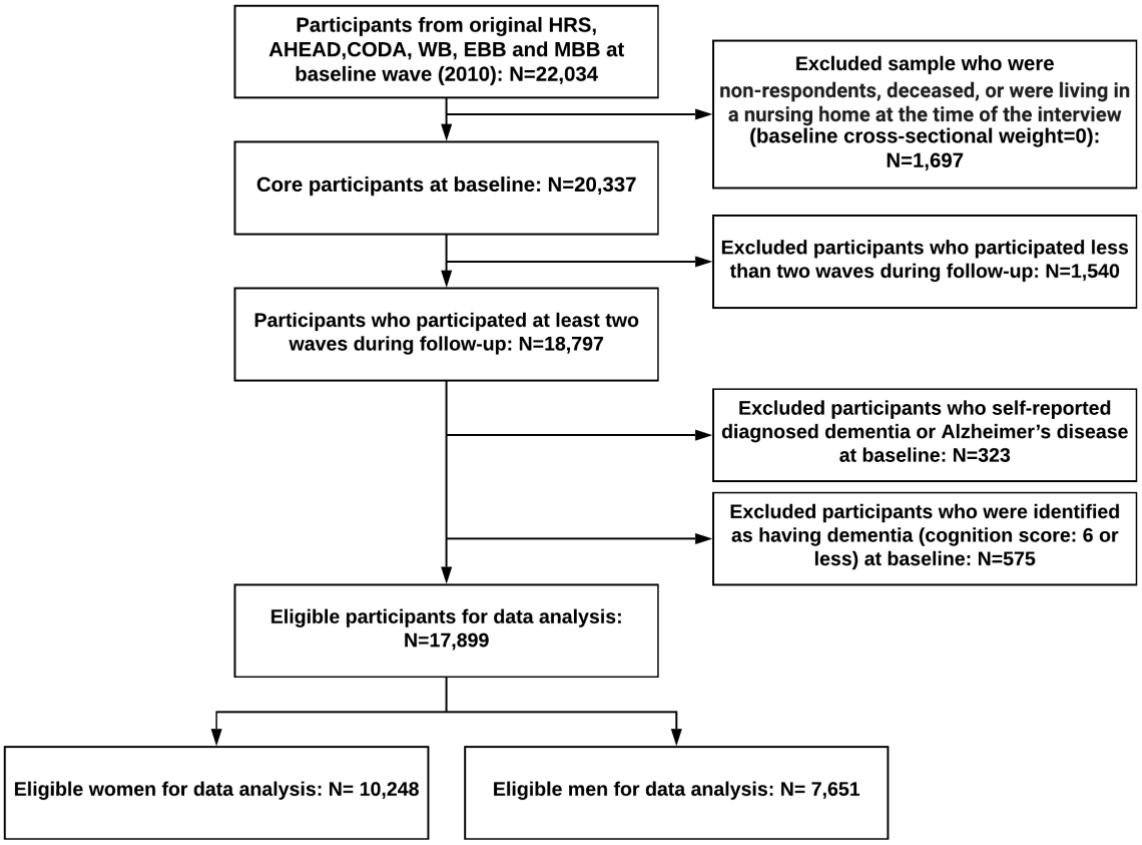
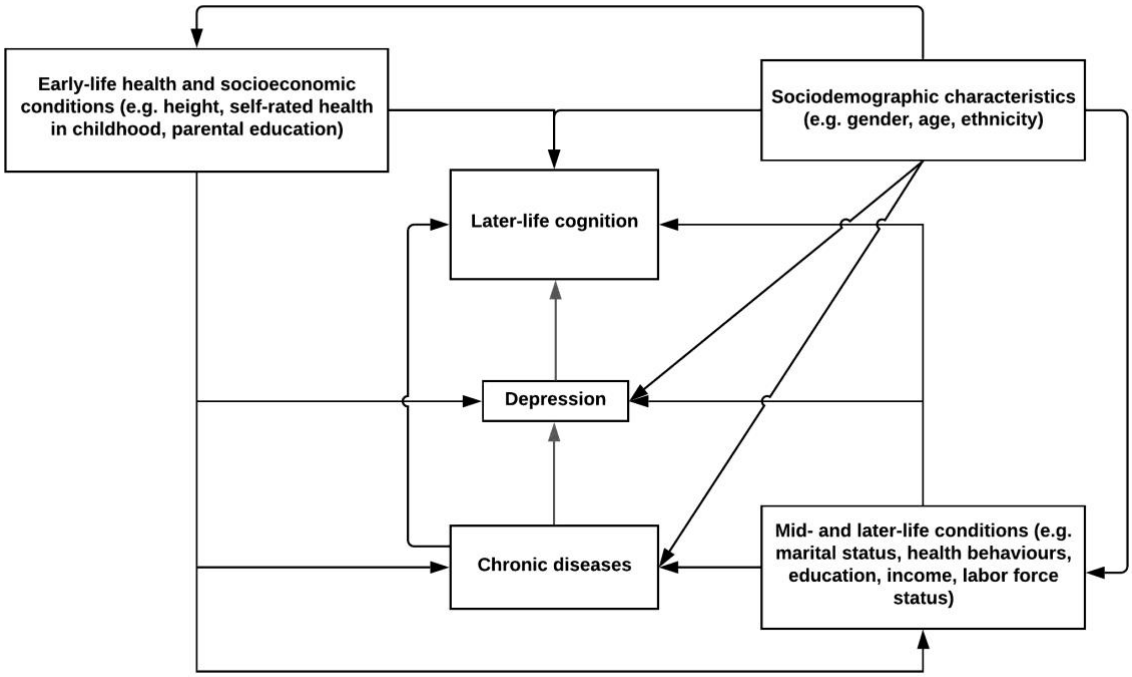
Figure 1 Procedure of sample selection



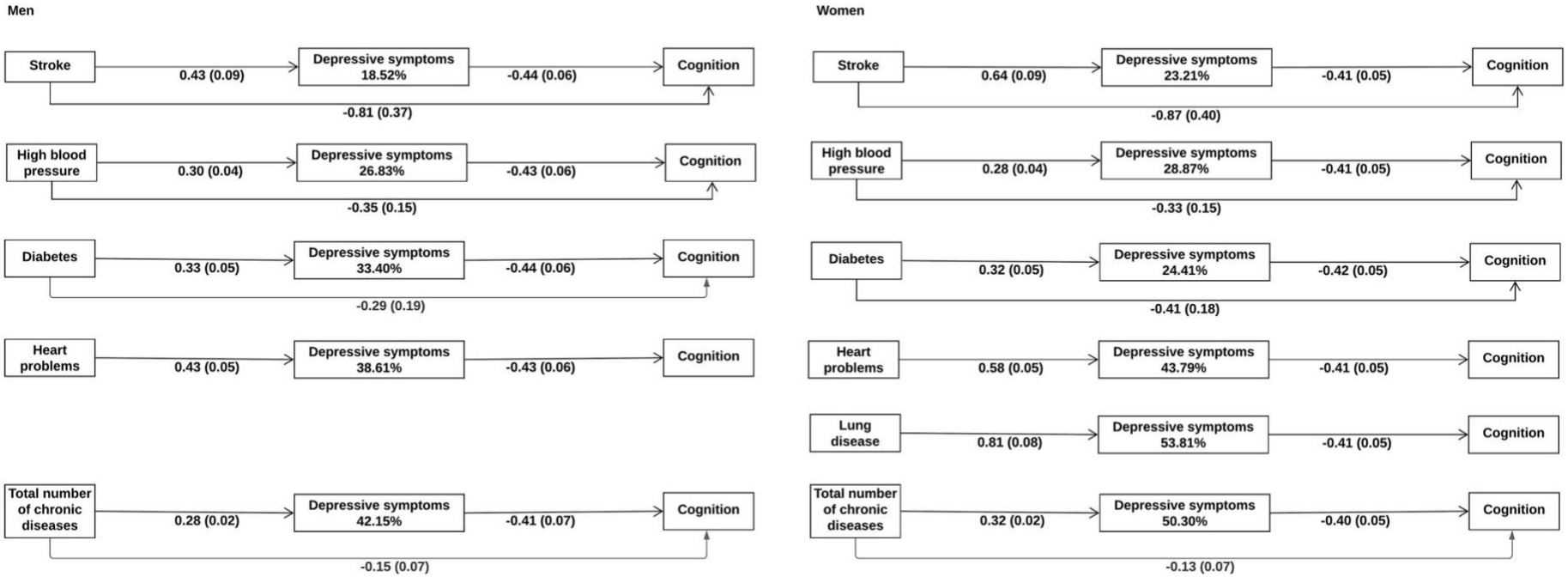
HRS: Health and Retirement Study; AHEAD: Asset and Health Dynamics among the Oldest Old; CODA: Children of the Depression; WB: War Baby; EBB: Early Baby Boomer; MBB: Mid Baby Boomer

Figure 2 Conceptual Framework showing the determinants of later-life cognition and the roles of chronic diseases and depression



Sources: adapted from Maurer (2010) and Socal and Trujillo (2018).

Figure 3 Illustration of mediation models among men and women



The illustration of the full mediation model showing all pathways from time-varying chronic diseases to time-varying cognition through the postulated time-varying mediators is very complex and difficult to visualise. Currently the Mplus does not support drawing complex path diagram for multilevel path analysis. The current figure summarizes regression coefficients with standard errors for the significant relationships between chronic diseases and cognition (direct effects), between chronic diseases and depression (indirect effects), and between depression and cognition (indirect effects); as well as the percentages of total effects mediated by depressive symptoms.

Table 1 Baseline sample characteristics among men and women

Variables	Men (N=7651)	Women (N=10248)
	Mean (SD)	**Mean (SD)**
Age	65 (10.3)	65 (10.6)
Cognition	15.1 (3.8)	16.4 (4.0)
Height (meters)	1.8 (0.01)	1.6 (0.01)
Depressive symptoms	1.2 (3.3)	1.5 (4.0)
	Median	**Median**
Income ($)	32948.1	25784.8
Total number of chronic diseases	2	2
Days of alcohol consumption per week	0	0
	%	**%**
Stroke		
No (Reference)	92.5	93.3
Yes	7.5	6.7
High blood pressure		
No (Reference)	45.6	46.3
Yes	54.4	53.7
Diabetes		
No (Reference)	75.7	78.7
Yes	24.3	21.3
Lung disease		
No (Reference)	92.0	90.0
Yes	8.0	10.0
Heart problems		
No (Reference)	77.2	81.6
Yes	22.8	18.4
Cancer		
No (Reference)	87.9	86.8
Yes	12.1	13.2
Arthritis		
No (Reference)	55.0	40.7
Yes	45.0	59.3
Ethnicity		
White/Caucasian (Reference)	84.0	83.6
Black/African American and others	16.0	16.4
Education		
First stage of tertiary education or above (Reference)	32.4	26.8
Upper secondary education	50.4	55.7
Lower secondary education	11.4	12.3
Primary education or below	6.0	5.2
Marital status		
Married/partnered (Reference)	76.7	55.2
Separated/divorced/single/spouse absent	16.9	23.0
Widowed	6.4	21.8
Smoking		
Non-smokers (Reference)	36.6	50.1
Ex-smokers	46.3	36.0
Current smokers	17.2	14.0

Days of alcohol consumption per week		
None	48.6	64.1
1 day	15.6	13.9
2 days	9.8	6.7
3 days	7.0	4.9
4 days	3.7	2.4
5 days	3.9	2.3
6 days	2.0	1.0
7 days	9.4	4.7
Vigorous physical activity		
Yes (Reference)	57.4	42.8
No	42.6	57.2
Labour force status		
Employed (Reference)	47.14	38.68
Retired	44.03	47.53
Disabled/unemployed/not in the labour force	8.83	13.79
Father's education (8+ years)		
Yes (Reference)	81.1	79.3
No	18.9	20.7
Mother's education (8+ years)		
Yes (Reference)	85.7	83.2
No	14.3	16.8
Self-reported health in childhood		
Best (Reference)	57.6	55.7
Good	24.4	23.2
Fair	13.5	14.5
Bad	3.9	5.0
Worst	0.6	1.6

Table 2 Regression coefficients with 95%CIs in basic and full models, for total, direct and indirect effects of chronic diseases on cognition in men

Estimates (95%CIs)	Total effects	Direct effects	Indirect effects via depressive symptoms	Intercepts
Basic model				
Stroke	-2.32 (-3.06, -1.58)	–	–	16.99 (16.84, 17.14)
High blood pressure	-1.17 (-1.49, -0.86)	–	–	17.53 (17.29, 17.77)
Diabetes	-1.31 (-1.69, -0.93)	–	–	17.18 (17.01, 17.34)
Heart problems	-0.66 (-1.07, -0.26)	–	–	16.99 (16.81, 17.16)
Lung disease	-1.39 (-2.01, -0.78)	–	–	16.94 (16.79, 17.09)
Cancer	0.22 (-0.33, 0.76)	–	–	16.77 (16.61, 16.94)
Arthritis	-0.56 (-0.88, -0.23)	–	–	17.09 (16.87, 17.30)
Total number of chronic diseases	-0.59 (-0.72, -0.46)	–	–	17.94 (17.65, 18.22)
Full model				
Stroke	-1.00 (-1.71, -0.29)	-0.81 (-1.53, -0.10)	-0.19 (-0.27, -0.10)	17.77 (14.53, 21.02)
High blood pressure	-0.47 (-0.77, -0.18)	-0.35 (-0.65, -0.04)	-0.13 (-0.18, -0.08)	17.67 (14.42, 20.91)
Diabetes	-0.43 (-0.80, -0.06)	-0.29 (-0.66, 0.09)	-0.14 (-0.20, -0.09)	17.73 (14.48, 20.97)
Heart problems	-0.48 (-0.87, -0.08)	-0.29 (-0.69, 0.11)	-0.18 (-0.25, -0.12)	17.45 (14.20, 20.69)
Lung disease	-0.20 (-0.81, 0.41)	0.06 (-0.56, 0.68)	-0.26 (-0.37, -0.16)	17.60 (14.36, 20.85)
Cancer	-0.02 (-0.52, 0.48)	0.09 (-0.41, 0.59)	-0.11 (-0.16, -0.05)	17.57 (14.33, 20.81)
Arthritis	-0.21 (-0.52, 0.10)	0.01 (-0.31, 0.32)	-0.22 (-0.29, -0.15)	17.62 (14.38, 20.87)
Total number of chronic diseases	-0.27 (-0.40, -0.14)	-0.15 (-0.29, -0.02)	-0.11 (-0.15, -0.08)	17.35 (14.09, 20.60)

Basic model: each model was adjusted for age only; full model: each model was adjusted for age, ethnicity, self-rated health in childhood, father's education, mother's education, height, marital status, education, income, labour force status, smoking, alcohol consumption and physical activity. Intercept is the predicted value of cognition for men when age=50. 95%CIs: 95% confidence intervals.

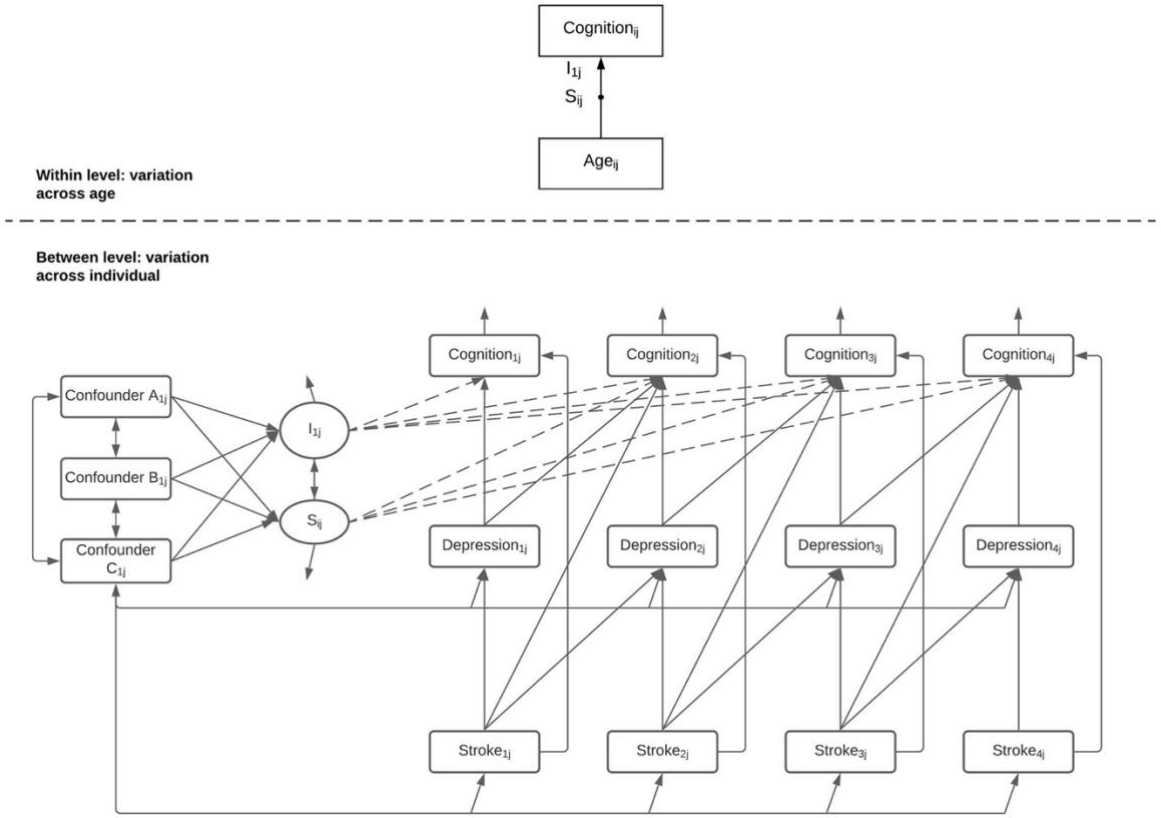
Table 3 Regression coefficients with 95%CIs in basic and full models, for total, direct and indirect effects of chronic diseases on cognition in women

Estimates (95%CIs)	Total effects	Direct effects	Indirect effects via depressive symptoms	Intercepts
Basic model				
Stroke	-2.67 (-3.35, -1.99)	–	–	17.51 (17.37, 17.64)
High blood pressure	-2.00 (-2.28, -1.71)	–	–	18.53 (18.32, 18.74)
Diabetes	-2.01 (-2.36, -1.66)	–	–	17.85 (17.70, 18.00)
Heart problems	-1.45 (-1.84, -1.06)	–	–	17.64 (17.48, 17.79)
Lung disease	-2.23 (-2.71, -1.74)	–	–	17.57 (17.43, 17.71)
Cancer	-0.04 (-0.48, 0.40)	–	–	17.31 (17.17, 17.46)
Arthritis	-0.68 (-0.99, -0.37)	–	–	17.75 (17.52, 17.97)
Total number of chronic diseases	-0.91 (-1.02, -0.79)	–	–	19.14 (18.88, 19.40)
Full model				
Stroke	-1.13 (-1.92, -0.35)	-0.87 (-1.66, -0.08)	-0.26 (-0.36, -0.17)	18.94 (16.23, 21.64)
High blood pressure	-0.44 (-0.72, -0.15)	-0.33 (-0.61, -0.04)	-0.11 (-0.16, -0.08)	18.96 (16.24, 21.68)
Diabetes	-0.55 (-0.90, -0.19)	-0.41 (-0.77, -0.06)	-0.13 (-0.19, -0.08)	19.25 (16.54, 21.96)
Heart problems	-0.54 (-0.93, -0.16)	-0.31 (-0.70, 0.09)	-0.24 (-0.31, -0.17)	18.83 (16.12, 21.54)
Lung disease	-0.62 (-1.13, -0.11)	-0.29 (-0.81, 0.23)	-0.33 (-0.44, -0.23)	18.91 (16.20, 21.62)
Cancer	-0.17 (-0.57, 0.22)	-0.10 (-0.50, 0.29)	-0.07 (-0.12, -0.03)	18.85 (16.14, 21.56)
Arthritis	0.03 (-0.26, 0.32)	0.32 (0.02, 0.62)	-0.29 (-0.36, -0.21)	18.80 (16.09, 21.51)
Total number of chronic diseases	-0.26 (-0.38, -0.13)	-0.13 (-0.26, 0.002)	-0.13 (-0.17, -0.09)	18.98 (16.27, 21.69)

Basic model: each model was adjusted for age only; full model: each model was adjusted for age, ethnicity, self-rated health in childhood, father's education, mother's education, height, marital status, education, income, labour force status, smoking, alcohol consumption and physical activity. Intercept is the predicted value of cognition for women when age=50; 95%CIs: 95% confidence intervals.

Supplementary documents

Figure S1 A hypothetical example of the multilevel path analysis



I: intercept; S: slope; i: wave; j: individual; one-way short arrow: residual; two-way arrow: covariance; At within level, time-varying age in each individual predicts an intercept and different slopes of the cognitive trajectories. At between level, time-invariant confounders as well as the covariances of the time-varying stroke and depression are factors of the variances in the random intercepts and slopes. Each individual has an intercept (I_{1j}) but random slopes (S_{ij}) of cognitive trajectories with increased age across waves. For the linear associations between stroke and cognition, stroke and depression, and depression and cognition, one independent variable in one wave predicts dependent variable within the same wave, and also the dependent variable in next wave beyond the prediction of the independent variable in next wave.

Table S1 Percentage of missingness in each variable by gender at each wave

	Men				**Women**			
Variables	**Wave 10 (N=7651)**	**Wave 11 (N=7467)**	**Wave 12 (N=6726)**	**Wave 13 (N=5857)**	**Wave 10 (N=10248)**	**Wave 11 (N=10054)**	**Wave 12 (N=9270)**	**Wave 13 (N=8282)**
Time-variant								
Age	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cognition	5.8	4.9	16.1	16.3	1.9	2.3	22.9	23.7
Stroke	0.0	0.0	0.1	0.4	0.0	0.0	0.1	0.6
High blood pressure	0.2	0.2	0.2	0.3	0.1	0.1	0.2	0.4
Diabetes	0.0	0.1	0.1	0.3	0.1	0.0	0.2	0.1
Lung disease	0.1	0.0	0.1	0.2	0.0	0.0	0.1	0.2
Heart problems	0.1	0.0	0.2	0.2	0.1	0.1	0.2	0.2
Cancer	0.1	0.1	0.2	0.2	0.1	0.1	0.1	0.1
Arthritis	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.2
Total number of chronic diseases	0.4	0.4	0.7	1.2	0.4	0.4	0.8	1.0
Depressive symptoms	5.8	5.0	5.5	6.7	1.9	2.3	3.0	5.0
Baseline								
Income	0.0	-	-	-	0.0	-	-	-
Marital status	0.0	-	-	-	0.0	-	-	-
Smoking	0.7	-	-	-	0.5	-	-	-
Days of alcohol consumption per week	0.3	-	-	-	0.2	-	-	-
Vigorous physical activity	0.2	-	-	-	0.2	-	-	-
Labour force status	0.0	-	-	-	0.0	-	-	-
Ethnicity	0.3	-	-	-	0.2	-	-	-
Education	0.0	-	-	-	0.0	-	-	-
Height	0.5	-	-	-	0.7	-	-	-
Father’s education (8+ years)	15.2	-	-	-	16.4	-	-	-
Mother’s education (8+ years)	9.7	-	-	-	8.4	-	-	-
Self-reported health in childhood	1.0	-	-	-	0.2	-	-	-

Table S2 Estimates of random effects in basic and full models in men

Estimates (95%CIs)	Within level (intercept)	Between level (intercept)	Between level (age)	Between level (covariance)
Basic model				
Stroke	6.70	8.91	0.001	-0.01
	(6.53, 6.87)	(7.83, 1.00)	(-0.002, 0.004)	(-0.08, 0.05)
High blood	6.71	8.86	0.001	-0.01
pressure	(6.53, 6.88)	(7.78, 9.95)	(-0.002, 0.004)	(-0.07, 0.05)
Diabetes	6.70	8.87	0.001	-0.01
	(6.53, 6.87)	(7.78, 9.97)	(-0.002, 0.004)	(-0.07, 0.05)
Heart problems	6.69	9.03	0.001	-0.01
	(6.52, 6.87)	(7.93, 10.13)	(-0.002, 0.004)	(-0.08, 0.05)
Lung disease	6.69	8.99	0.001	-0.01
	(6.52, 6.87)	(7.90, 10.09)	(-0.002, 0.004)	(-0.08, 0.05)
Cancer	6.70	9.09	0.001	-0.01
	(6.52, 6.87)	(7.99, 10.19)	(-0.002, 0.004)	(-0.08, 0.05)
Arthritis	6.69	9.06	0.001	-0.01
	(6.52, 6.86)	(7.96, 10.16)	(-0.002, 0.004)	(-0.08, 0.05)
Total number of	6.70	8.79	0.001	-0.01
chronic diseases	(6.53, 6.87)	(7.71, 9.88)	(-0.002, 0.004)	(-0.07, 0.05)
Full model				
Stroke	6.59	4.56	0.001	0.003
	(6.41, 6.78)	(3.71, 5.41)	(-0.001, 0.004)	(-0.05, 0.05)
High blood	6.60	4.56	0.001	0.005
pressure	(6.41, 6.79)	(3.70, 5.41)	(-0.002, 0.004)	(-0.05, 0.05)
Diabetes	6.60	4.55	0.001	0.005
	(6.41, 6.78)	(3.70, 5.41)	(-0.002, 0.004)	(-0.05, 0.06)
Heart problems	6.59	4.56	0.001	0.005
	(6.40, 6.77)	(3.70, 5.42)	(-0.002, 0.004)	(-0.05, 0.06)
Lung disease	6.59	4.56	0.001	0.005
	(6.40, 6.77)	(3.71, 5.42)	(-0.002, 0.004)	(-0.05, 0.05)
Cancer	6.59	4.57	0.001	0.005
	(6.41, 6.78)	(3.71, 5.43)	(-0.002, 0.004)	(-0.05, 0.06)
Arthritis	6.59	4.57	0.001	0.005
	(6.41, 6.78)	(3.71, 5.43)	(-0.002, 0.004)	(-0.05, 0.06)
Total number of	6.60	4.57	0.001	0.004
chronic diseases	(6.41, 6.78)	(3.71, 5.43)	(-0.002, 0.004)	(-0.05, 0.06)

Basic model: each model was adjusted for age only; full model: each model was adjusted for age, ethnicity, self-rated health in childhood, father's education, mother's education, height, marital status, education, income, labour force status, smoking, alcohol consumption and physical activity. Within level (intercept): residual variance of cognition within men; Between level (intercept): the variance of the intercept; Between level (age): the variance of the slope for age; and Between level (covariance): the covariance of the intercept and slope. 95%CIs: 95% confidence intervals.

Table S3 Estimates of random effects in basic and full models in women

Estimates (95%CIs)	Within level (intercept)	Between level (intercept)	Between level (age)	Between level (covariance)
Basic model				
Stroke	7.69 (7.51, 7.86)	10.51 (9.48, 11.55)	0.001 (-0.002, 0.004)	-0.03 (-0.09, 0.03)
High blood pressure	7.69 (7.52, 7.87)	9.99 (8.96, 11.02)	0.001 (-0.002, 0.004)	-0.02 (-0.08, 0.03)
Diabetes	7.68 (7.51, 7.85)	10.37 (9.34, 11.40)	0.001 (-0.001, 0.004)	-0.04 (-0.09, 0.02)
Heart problems	7.70 (7.52, 7.87)	10.55 (9.50, 11.60)	0.001 (-0.001, 0.004)	-0.03 (-0.09, 0.03)
Lung disease	7.69 (7.52, 7.87)	10.50 (9.45, 11.55)	0.001 (-0.001, 0.004)	-0.03 (-0.09, 0.03)
Cancer	7.69 (7.52, 7.86)	10.74 (9.68, 11.80)	0.001 (-0.002, 0.004)	-0.03 (-0.09, 0.03)
Arthritis	7.69 (7.52, 7.86)	10.64 (9.59, 11.70)	0.001 (-0.002, 0.004)	-0.03 (-0.09, 0.03)
Total number of chronic diseases	7.67 (7.50, 7.84)	9.94 (8.92, 10.95)	0.001 (-0.002, 0.004)	-0.03 (-0.08, 0.03)
Full model				
Stroke	7.54 (7.36, 7.73)	5.17 (4.38, 5.97)	0.002 (-0.001, 0.004)	0.01 (-0.05, 0.04)
High blood pressure	7.55 (7.36, 7.74)	5.18 (4.38, 5.91)	0.002 (-0.001, 0.004)	0.01 (-0.06, 0.04)
Diabetes	7.55 (7.36, 7.73)	5.19 (4.39, 5.99)	0.002 (-0.001, 0.004)	0.01 (-0.06, 0.04)
Heart problems	7.56 (7.37, 7.75)	5.16 (4.37, 5.96)	0.002 (-0.001, 0.004)	-0.01 (-0.05, 0.04)
Lung disease	7.55 (7.37, 7.74)	5.18 (4.38, 5.98)	0.002 (-0.001, 0.004)	-0.01 (-0.05, 0.04)
Cancer	7.56 (7.37, 7.74)	5.17 (4.37, 5.96)	0.002 (-0.001, 0.004)	-0.01 (-0.05, 0.04)
Arthritis	7.55 (7.37, 7.74)	5.15 (4.36, 5.95)	0.002 (-0.001, 0.004)	-0.01 (-0.05, 0.04)
Total number of chronic diseases	7.53 (7.35, 7.72)	5.19 (4.39, 5.98)	0.002 (-0.001, 0.004)	-0.01 (-0.06, 0.04)

*Basic model: each model was adjusted for age only; full model: each model was adjusted for age, ethnicity, self-rated health in childhood, father's education, mother's education, height, marital status, education, income, labour force status, smoking, alcohol consumption and physical activity.*It is the predicted value of cognition for women when age=50; Within level (intercept): residual variance of cognition within women; Between level (intercept): the variance of the intercept; Between level (age): the variance of the slope for age; and Between level (covariance): the covariance of the intercept and slope. 95%CIs: 95% confidence intervals.*

Table S4 Standardised estimates of causation in Cross-Lagged models by gender and types of chronic diseases

	Stroke	**High blood pressure**	**Diabetes**	**Heart problems**	**Lung disease**	**Total number of chronic diseases**
Men	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**
Depressive symptoms 12 » Cognition 13	**-0.152 (0.039)**	**-0.151 (0.039)**	**-0.151 (0.039)**	**-0.151 (0.039)**	-	**-0.151 (0.040)**
Depressive symptoms 11 » Cognition 12	-0.042 (0.041)	-0.041 (0.041)	-0.041 (0.041)	-0.041 (0.041)	-	-0.041 (0.041)
Depressive symptoms 10 » Cognition 11	-0.042 (0.033)	-0.042 (0.033)	-0.043 (0.033)	-0.042 (0.033)	-	-0.043 (0.033)
Chronic disease 12 » Depressive symptoms 13	**0.224 (0.110)**	0.002 (0.052)	**0.212 (0.067)**	**0.240 (0.064)**	-	**0.090 (0.023)**
Chronic disease 11 » Depressive symptoms 12	0.090 (0.102)	0.031 (0.051)	**0.107 (0.062)**	**0.186 (0.064)**	-	**0.078 (0.024)**
Chronic disease 10 » Depressive symptoms 11	0.170 (0.111)	**0.126 (0.052)**	0.097 (0.062)	**0.125 (0.060)**	-	**0.089 (0.022)**
Women	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**
Depressive symptoms 12 » Cognition 13	0.009 (0.037)	0.005 (0.037)	0.009 (0.037)	0.007 (0.037)	0.007 (0.037)	0.006 (0.037)
Depressive symptoms 11 » Cognition 12	**-0.107 (0.028)**	**-0.108 (0.028)**	**-0.107 (0.028)**	**-0.107 (0.028)**	**-0.108 (0.028)**	**-0.108 (0.028)**
Depressive symptoms 10 » Cognition 11	**-0.059 (0.025)**	**-0.059 (0.025)**	**-0.059 (0.025)**	**-0.058 (0.025)**	**-0.059 (0.025)**	**-0.056 (0.025)**

Chronic disease 12 » Depressive symptoms 13	0.186 (0.120)	**0.099 (0.053)**	0.039 (0.068)	**0.281 (0.071)**	**0.415 (0.108)**	**0.105 (0.023)**
Chronic disease 11 » Depressive symptoms 12	0.116 (0.100)	0.047 (0.049)	0.053 (0.060)	**0.138 (0.063)**	**0.225 (0.095)**	**0.092 (0.021)**
Chronic disease 10 » Depressive symptoms 11	**0.207 (0.106)**	**0.162 (0.048)**	**0.147 (0.064)**	0.095 (0.059)	**0.247 (0.093)**	**0.104 (0.021)**

Estimates in bold are for statistically significant relationships; S.E.: standard error; the Cross-Lagged analysis for lung disease in men was not conducted due to the non-significant total effect of lung disease on cognition in the main analysis.

Table S5 Standardised estimates of reverse causation in Cross-Lagged models by gender and types of chronic diseases

	Stroke	**High blood pressure**	**Diabetes**	**Heart problems**	**Lung disease**	**Total number of chronic diseases**
Men	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**
Cognition 12 » Depressive symptoms 13	-0.009 (0.007)	-0.010 (0.007)	-0.010 (0.007)	-0.009 (0.007)	-	-0.007 (0.007)
Cognition 11 » Depressive symptoms 12	**-0.021 (0.008)**	**-0.022 (0.007)**	**-0.022 (0.007)**	**-0.021 (0.007)**	-	**-0.021 (0.007)**
Cognition 10 » Depressive symptoms 11	0.002 (0.010)	0.001 (0.008)	0.002 (0.007)	0.002 (0.008)	-	0.004 (0.008)
Depressive symptoms 12 » Chronic disease 13	0.002 (0.002)	-0.002 (0.003)	0.001 (0.003)	-0.001 (0.003)	-	0.002 (0.007)
Depressive symptoms 11 » Chronic disease 12	0.004 (0.002)	0.001 (0.003)	0.001 (0.002)	0.004 (0.002)	-	0.012 (0.007)
Depressive symptoms 10 » Chronic disease 11	0.000 (0.001)	0.000 (0.003)	0.002 (0.002)	0.001 (0.002)	-	0.008 (0.007)
Women	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**	**Estimate (S.E.)**
Cognition 12 » Depressive symptoms 13	**-0.016 (0.007)**	**-0.015 (0.007)**	**-0.016 (0.007)**	**-0.015 (0.007)**	**-0.016 (0.007)**	-0.014 (0.007)
Cognition 11 » Depressive symptoms 12	-0.010 (0.007)	-0.010 (0.007)	-0.010 (0.007)	-0.010 (0.007)	-0.010 (0.007)	-0.008 (0.007)
Cognition 10 » Depressive symptoms 11	-0.013 (0.007)	-0.012 (0.007)	-0.013 (0.007)	-0.013 (0.007)	-0.013 (0.007)	-0.011 (0.007)

Depressive symptoms 12 » Chronic disease 13	0.002 (0.001)	0.004 (0.002)	0.000 (0.002)	0.003 (0.002)	0.003 (0.001)	**0.017 (0.005)**
Depressive symptoms 11 » Chronic disease 12	0.002 (0.001)	-0.001 (0.001)	0.002 (0.001)	0.000 (0.002)	0.001 (0.002)	0.005 (0.004)
Depressive symptoms 10 » Chronic disease 11	0.002 (0.001)	-0.001 (0.001)	0.001 (0.002)	0.003 (0.002)	0.002 (0.001)	**0.009 (0.004)**

Estimates in bold are for statistically significant relationships; S.E.: standard error; the Cross-Lagged analysis for lung disease in men was not conducted due to the non-significant total effect of lung disease on cognition in the main analysis.

Table S6 Multilevel logistic regression for the associations between chronic diseases (binary), high-risk depressive symptoms (binary), and cognitive impairment/dementia (binary), and between chronic diseases (binary) and high-risk depressive symptoms (binary); as well as proportions of indirect effects of high-risk depressive symptoms in men and women, separately

	ORs (95%CIs)	Indirect effect (%)
Men (N=7651)		
Stroke		
Direct effect: Stroke → cognitive impairment/dementia	2.01 (1.57, 2.57)	16.54
Indirect effect: HD → cognitive impairment/dementia	1.20 (1.01, 1.55)	
Indirect effect: Stroke → HD	2.08 (1.51, 2.87)	
High blood pressure		
Direct effect: High blood pressure → Cognitive impairment/dementia	1.37 (1.18, 1.59)	25.60
Indirect effect: HD → Cognitive impairment/dementia	1.24 (1.02, 1.60)	
Indirect effect: High blood pressure → HD	1.63 (1.30, 2.04)	
Diabetes		
Direct effect: Diabetes → Cognitive impairment/dementia	1.39 (1.18, 1.64)	27.37
Indirect effect: HD → Cognitive impairment/dementia	1.24 (1.02, 1.60)	
Indirect effect: Diabetes → HD	1.76 (1.40, 2.20)	
Heart problems		
Direct effect: Heart problems → Cognitive impairment/dementia	1.24 (1.05, 1.47)	36.31
Indirect effect: HD → Cognitive impairment/dementia	1.24 (1.02, 1.59)	
Indirect effect: Heart problems → HD	1.76 (1.41, 2.20)	
Lung disease		
Direct effect: Lung disease → Cognitive impairment/dementia	1.10 (0.85, 1.42)	-
Indirect effect: HD → Cognitive impairment/dementia	1.24 (0.96, 1.60)	

Indirect effect: Lung disease → HD	2.21 (1.61, 3.02)	
Cancer		
Direct effect: Cancer → Cognitive impairment/dementia	1.26 (1.04, 1.54)	-
Indirect effect: HD → Cognitive impairment/dementia	1.24 (0.96, 1.60)	
Indirect effect: Cancer → HD	1.49 (1.15, 1.94)	
Arthritis		
Direct effect: Arthritis → Cognitive impairment/dementia	1.05 (0.90, 1.22)	-
Indirect effect: HD → Cognitive impairment/dementia	1.23 (0.96, 1.59)	
Indirect effect: Arthritis → HD	2.00 (1.60, 2.48)	
Total number of chronic diseases (comorbidity)		
Direct effect: Comorbidity → Cognitive impairment/dementia	1.12 (1.05, 1.19)	43.89
Indirect effect: HD → Cognitive impairment/dementia	1.22 (1.01, 1.57)	
Indirect effect: Comorbidity → HD	1.54 (1.41, 1.69)	
Women (N=10248)		
Direct effect: Stroke → Cognitive impairment/dementia	2.49 (2.00, 3.10)	20.63
Indirect effect: HD → Cognitive impairment/dementia	1.74 (1.47, 2.06)	
Indirect effect: Stroke → HD	1.54 (1.21, 1.95)	
High blood pressure		
Direct effect: High blood pressure → Cognitive impairment/dementia	1.42 (1.25, 1.62)	25.69
Indirect effect: HD → Cognitive impairment/dementia	1.73 (1.46, 2.06)	
Indirect effect: High blood pressure → HD	1.25 (1.08, 1.45)	
Diabetes		

Direct effect: Diabetes → Cognitive impairment/dementia	1.23 (1.07, 1.42)	52.38
Indirect effect: HD → Cognitive impairment/dementia	1.73 (1.46, 2.01)	
Indirect effect: Diabetes → HD	1.52 (1.30, 2.05)	
Heart problems		
Direct effect: Heart problems → Cognitive impairment/dementia	1.61 (1.40, 1.86)	37.35
Indirect effect: HD → Cognitive impairment/dementia	1.72 (1.45, 2.04)	
Indirect effect: Heart problems → HD	1.70 (1.46, 1.98)	
Lung disease		
Direct effect: Lung disease → Cognitive impairment/dementia	1.22 (1.001, 1.49)	70.86
Indirect effect: HD → Cognitive impairment/dementia	1.71 (1.45, 2.04)	
Indirect effect: Lung disease → HD	2.46 (2.03, 2.98)	
Cancer		
Direct effect: Cancer → Cognitive impairment/dementia	1.09 (0.92, 1.29)	-
Indirect effect: HD → Cognitive impairment/dementia	1.73 (1.46, 2.05)	
Indirect effect: Cancer → HD	1.17 (0.97, 1.41)	
Arthritis		
Direct effect: Arthritis → Cognitive impairment/dementia	1.05 (0.92, 1.19)	-
Indirect effect: HD → Cognitive impairment/dementia	1.73 (1.46, 2.05)	
Indirect effect: Arthritis → HD	1.55 (0.96, 2.25)	
Total number of chronic diseases (comorbidity)		
Direct effect: Comorbidity → Cognitive impairment/dementia	1.16 (1.10, 1.24)	55.93
Indirect effect: HD → Cognitive impairment/dementia	1.76 (1.44, 2.15)	

Indirect effect: Comorbidity → HD	1.41 (1.32, 1.51)

95%CI: 95% confidence interval; HD: high-risk depressive symptoms; *Each model was adjusted for age, ethnicity, self-rated health in childhood, father's education, mother's education, height, marital status, education, income, labour force status, smoking, alcohol consumption and physical activity. The proportion of indirect effect of high-risk depressive symptoms was calculated using equation ((ln (OR* $_{HD \rightarrow Cognitive\ impairment/dementia}$ *) x ln (OR* $_{Chronic\ disease \rightarrow HD}$ *)) / ((ln (OR* $_{HD \rightarrow Cognitive\ impairment/dementia}$ *) x ln (OR* $_{Chronic\ disease \rightarrow HD}$ *) + ln (OR* $_{Chronic\ disease \rightarrow Cognitive\ impairment/dementia}$ *))) x 100; We calculated the proportions of indirect effect when the two ORs for indirect effects were both statistically significant.*

Note: Multilevel path analysis does not allow for the inclusion of binary/categorical dependent variable and so does not lend itself to straightforward interpretation. Multilevel logistic regression with random effects does not have these restrictions and through estimating ORs, it can provide better measures for interpreting the finding. However, the estimates obtained using binary mediator and outcome variables could be biased. Whilst estimations based on the 'product method' to estimate indirect effects of an exposure on an outcome are stable for assessing mediation with binary outcomes with sample sizes larger than 500 (MacKinnon et al. 2007), VanderWeele argued that neither this 'product method' nor 'difference method' was valid for estimating the direct and indirect effects of an exposure when outcome variables were binary (VanderWeele 2016). When having a binary outcome Y, there was unobserved continuous variable Y underlying binary Y, and the variance of Y* is unknown; while when having a continuous outcome Y, the variance of outcome Y is known, which is fixed across models with difference covariates (Heron, Brown, and Croudace 2012). If the binary outcome is not rare (10% is usually the cut-off: and in our case, 18% of the analytical sample were classified as having dementia/cognitive impairment over time), estimations for the mediation effects of binary mediators generated by different types of mediation analysis could be very different (VanderWeele 2016).*