Dementia
and Geriatric
Cognitive Disorders

Risk Factors of Transition from Normal Cognition to Mild Cognitive Disorder: The PATH through Life Study

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Abstract

Aims: The aim of this study was to identify physical and mental health and lifestyle predictors of transition from normal cognition to mild cognitive disorder (MCD). *Methods:* A total of 2,082 individuals, aged 60–64 years, were assessed at 2 time-points 4 years apart for mild cognitive impairment (MCI) and other MCDs. *Results:* The main predictors of conversion to MCI and to other mild cognitive disorders were past alcohol intake, current anxiety and depression medication, increased systolic blood pressure, and past smoking. *Conclusion:* Participants with a history of smoking or harmful alcohol consumption, hypertension, or who took medication for anxiety or depression were at increased risk of transitioning to MCI or any MCD. Strategies targeted at managing the above risk factors may have benefits in preventing mild cognitive decline in relatively healthy middle-aged individuals living in the community.

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Introduction

There is considerable evidence for an association between mild cognitive disorders (MCDs) in ageing and Alzheimer's disease (AD) [1], with many studies showing high rates (~30%) of conversion from MCD to AD over relatively short periods of time (2–5 years) [2]. However, few studies have reported on factors predicting transition from normal cognitive ageing to clinically assessed MCD or on factors protecting individuals from such a transition, and those who did generally assessed older individuals [3]. Based on post-mortem studies, Braak et al. [4] have shown that the neurodegenerative processes leading to AD start early in adulthood and progress over decades. It may follow that known risk factors for conversion to dementia are also predictive of conversion to MCD and, therefore, might be amenable to even earlier intervention.

With the aim of identifying these factors in younger individuals, we investigated a community-based cohort of 60–64-year-old participants taking part in a large prospective longitudinal study of ageing. We expected, aside from age, cardiovascular disease [5], diabetes [6], obesity [7], head injury [8], hypercholesterolemia [9], excessive alcohol consumption [10], depression [11], smoking [12],

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poor visual acuity [13], and APOE*E4 genotype [14] to increase the risk, and moderate alcohol consumption, physical fitness (forced expiratory and vital capacity), handgrip, mental well-being, and APOE*E2 genotype to be protective factors.

One problem in such research relates to the lack of a single universally acceptable definition of MCD as a pro-drome to AD. While the MCI definition proposed by the International Consensus Conference is widely used, the concept is not very stable especially in individuals in their 60s, with a large proportion of those assessed reverting to a non-MCI status at follow-up [15, 16]. In contrast, we have shown the stability of the classification with any mild cognitive disorders, i.e. any of Age Associated Memory Impairment (AAMI), Age Associated Cognitive Decline (AACD), Mild Neurocognitive Disorder (MNC) or MCI, to be high (~89%) [16]. For this reason, we investigated the predictors for both MCI and any MCD (any-MCD) in the present study.

Methods

Study Population
The design of the PATH Through Life Study has been described elsewhere [17] as has the clinical sub-study [18]. Briefly, participants who were residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, were recruited randomly through the electoral roll to participate in a study interested in the risk and protective factors for normal ageing, dementia and other neuropsychiatric disorders. Enrolment to vote is compulsory for Australian citizens. Participants were recruited in the 3 age cohorts 20–24, 40–44, and 60–64 and are to be followed every 4 years, over a total period of 20 years. The study was approved by the Australian National University Ethics Committee. Results presented here concern the first- and second-wave interviews with 60–64-year-olds which were conducted in 2001–2002 and 2005–2006. Of 4,831 people contacted, 2,551 (58.3%) were interviewed in wave 1. Of these, 2,222 individuals completed wave 2 assessments. A further 139 participants were excluded from analysis because they were either diagnosed with a cognitive disorder at wave 1 (n = 75) or refused dementia assessment after screening positive on cognitive impairment measures (n = 64). One participant was excluded due to the loss of wave 1 measures (fig. 1).

Clinical Assessment
The screening procedures and clinical diagnosis for wave 1 and wave 2 have been described previously [9, 16, 18]. In brief, diagnoses were obtained for MCI [19], AAMI [20], AACD [21], MNC [22], impairment on the clinical dementia rating (CDR = 0.5) [23], and other cognitive disorder (OCD) using published criteria [24]. DSM-IV criteria [22] were used to assess dementia and the same assessment procedure was used at wave 1 and 2.

As we have previously reported high stability of diagnosis of any mild cognitive disorder (i.e. MNC, OCD, AAMI, MCI, AACD)
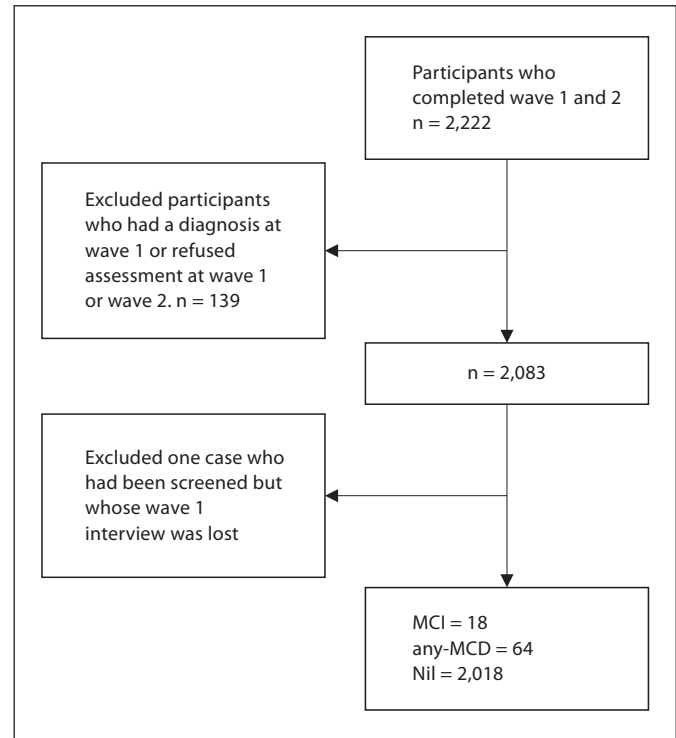
over a 4-year follow-up [16], participants were also classified with any-MCD and analyses were conducted to identify predictors of this more general classification.

Physical Health Measures
Diastolic and systolic blood pressure (continuous measures) were measured twice while seated and after a rest period during the interview. Self-reported diabetes and diabetes medication were recorded (no = 0/yes = 1). Forced vital capacity (FVC, continuous) was measured using the forced expiratory vital capacity maneuver with a spirometer (Micro Spirometer, Micro Medical Ltd., Rochester, UK) using the best of 3 attempts. Physical health was measured with the SF-12, a validated 12-item self-administered inventory based on which physical and mental health components can be computed with higher scores reflecting better health [25]. Self-reported measures of weight and height were used to compute a body mass index (BMI, continuous) measure. Stroke, and arthritis were assessed by self-report (no = 0/yes = 1). APOE status was assessed by buccal swabs and is described elsewhere [26].

Mental Health Measures
Self-rated mental health was measured by the component summary of the SF-12, with higher scores reflecting better health [25]. Anxiety and depression symptoms in the past month were assessed by the Goldberg anxiety/depression scales which consist of an 18-item self-report symptom inventory with higher scores reflecting more anxiety/depression symptoms [27].

Fig. 1. Sample selection.

Medications

Information on type and number of current medications was recorded. Medication for hypertension, diabetes, hypercholesterolemia, anxiety, and depression (no = 0/yes = 1) were examined, as these conditions have previously been associated with cognitive decline [28].

Lifestyle Measures

Alcohol consumption was assessed using the Alcohol Use Disorders Identification Test [AUDIT; 29]. Categorical estimates of weekly consumption were derived from the quantity and frequency items of the AUDIT. For men, weekly alcohol consumption was categorized from 1–6 as abstainer, light (1–13 units), moderate (14–27 units), hazardous (28–42 units), or harmful (>42 units) (i.e. 1 = abstainer; 6 = harmful). For women, weekly alcohol consumption was divided into abstainer, light (1–7 units), moderate (8–13 units), hazardous (14–28 units) or harmful (>28 units) categories where a unit equates 10 g of pure alcohol. Weekly consumption of standard drinks was estimated from items measuring reported frequency of alcohol intake, and the number of standard drinks consumed on typical drinking days, following quantity-frequency assessment procedures. Current and past smoking habits were recorded (no = 0/yes = 1).

Statistical Analysis

Group differences were assessed using χ^2 tests for categorical variables and t tests for continuous variables. Logistic regression analysis was used to identify significant predictors of binary group membership (normal vs. MCI/any-MCD) using a stepwise approach. In the first phase, each health and lifestyle variable was assessed in a univariate analysis while controlling for age, sex, and education. In the second phase, multivariate logistic regression analyses were conducted to determine which variables had the highest predictive value. All variables were entered together and the model was progressively reduced until it only included significant predictors after controlling for age, sex, and education. The alpha level was set at p = 0.05. Sex interactions were investigated.

Results

Table 1 presents the demographic, clinical, and genetic characteristics of the study groups (normal, MCI, and any-MCD). Eighteen MCI and 64 any-MCD (18 MCI, 24 AAMI, 14 MNC, 3 OCD, and 63 impaired on CDR) individuals were identified from the 2,082 participants with no diagnosis at wave 1. No case of dementia was identified.

Predictors of Conversion to MCI

FVC (odds ratio (OR) 0.45; 95% confidence interval (CI) 0.44–0.46; p = 0.029), anxiety medication (OR 4.08; 95% CI 1.16–14.39; p = 0.029), anti-depressive medication (OR 4.12; 95% CI 1.16–14.64; p = 0.029), and alcohol abstinence (OR 9.10; 95% CI 3.02–27.42; p < 0.001) were sig-

nificant predictors of conversion to MCI identified by univariate logistic analyses while controlling for sex, age, and education (table 2). When all variables were assessed in a single multivariate analysis, and after reduction of the model, past alcohol intake (OR 0.59; 95% CI 0.37–0.92; p = 0.021), quadratic trend for past alcohol intake (modelling a U-shape and indicating a higher risk for low and high drinking categories: OR 1.58; 95% CI 1.18–2.11; p = 0.002), and past smoking (OR 3.22; 95% CI 1.05–9.87; p = 0.041) were significant predictors of conversion to MCI (table 3). Trends were also detected for anxiety medication (OR 3.58; 95% CI 0.97–13.22; p = 0.056), visual acuity (OR 0.92; 95% CI 0.85–1.00; p = 0.059), and APOE*E2 genotype (OR 2.74; 95% CI 0.95–7.97; p = 0.063). APOE*E4 *APOE* genotype was not a significant predictor of conversion to MCI. None of the sex interactions reached significance.

Predictors of Conversion to Any-MCD

Taking antidepressant medication (OR 3.71; 95% CI 1.76–7.81; p = 0.001), past smoking (OR 1.78; 95% CI 1.06–3.00; p = 0.031), arthritis (OR 1.73; 95% CI 1.04–2.90; p = 0.037), depression (OR 1.15; 95% CI 1.02–1.29; p = 0.026), BMI (OR 1.05; 95% CI 1.05–1.09; p = 0.025), physical health (SF-12, OR 0.97; 95% CI 0.95–0.99; p = 0.011), taking cholesterol-lowering medication (OR 2.01; 95% CI 1.20–3.37; p = 0.008) and oral diabetes medication (OR 2.87; 95% CI 1.26–6.53; p = 0.012) were significant predictors of conversion to any-MCD identified by univariate logistic analyses while controlling for sex, age, and education (table 2). When all variables were assessed in a single multivariate analysis, and after reduction of the model, diastolic blood pressure (OR 0.96; 95% CI 0.92–0.99; p = 0.011), past smoking (OR 1.97; 95% CI 1.12–3.44; p = 0.018), taking depression medication (OR 3.25; 95% CI 1.51–7.00; p = 0.003) and past alcohol intake category (OR 0.75; 95% CI 0.57–1.00; p = 0.046) were significant predictors of conversion to MCI (table 4). Trends were also detected for BMI (OR 1.04; 95% CI 1.00–1.08; p = 0.054), systolic blood pressure (OR 1.02; 95% CI 1.00–1.04; p = 0.057), and a quadratic trend for past alcohol intake (modelling a U-shape and indicating a higher risk for low and high drinking categories: OR 1.17; 95% CI 0.98–1.40; p = 0.087). Neither *E4 nor *E2 *APOE* genotype were significant predictors of conversion to MCI. None of the sex interactions reached significance.

Table 1. Demographic, clinical, and genetic characteristics of normal, MCI, and any-MCD sub-samples at baseline (wave 1)

	Normal at wave 2 (n = 2,018)	MCI at wave 2 (n = 18)	Any-MCD at wave 2 (n = 64)
Females, n	996 (49.2%)	8 (44.4%)	24 (40.7%)
Age at wave 1, years	62.53 ± 1.51	62.22 ± 1.77	62.53 ± 1.63
Education, years	14.05 ± 2.67	13.11 ± 2.15	13.13 ± 2.36**
Caucasian	1,850 (96.60%)	15 (83.30%)*	60 (93.80%)
English-speaking	1,822 (90.30%)	12 (66.70%)**	54 (84.40%)
MMSE			
At wave 1	29.37 ± 0.895	29.11 ± 0.83**	28.92 ± 0.981**
At wave 2	29.33 ± 0.96	27.5 ± 1.65**	27.94 ± 1.84**
APOE*E4 carriers	526 (26.06%)	3 (16.70%)	12 (18.75%)
APOE*E2 carriers	278 (13.78%)	5 (27.78%)	11 (17.20%)
Diabetes	135 (6.70%)	1 (5.60%)	9 (14.10%)*
Taking oral diabetes medication	77 (3.80%)	1 (5.60%)	7 (10.90%)*
Taking cholesterol-lowering medication	467 (23.10%)	4 (22.20%)	25 (39.10%)**
Taking blood pressure medication	633 (31.40%)	7 (38.90%)	28 (43.80%)*
Stroke	72 (3.60%)	0 (0.00%)	5 (7.80%)
Head injury	107 (5.30%)	0 (0.00%)	6 (9.40%)
Arthritis	682 (33.80%)	9 (50.00%)	30 (46.90%)*
Taking anxiety medication	93 (4.60%)	3 (16.70%)*	5 (7.80%)
Taking depression medication	93 (4.60%)	3 (16.70%)*	9 (14.10%)**
Taking memory medication	59 (2.90%)	1 (5.60%)	2 (3.10%)
Goldberg depression scale	1.54 ± 1.79	2.08 ± 1.98	2.28 ± 2.30*
Goldberg anxiety scale	2.14 ± 2.24	2.33 ± 2.34	2.06 ± 2.36
Past alcohol intake categories			
Abstainer	93 (4.60%)	5 (27.80%)**	6 (9.40%)
Occasional	462 (22.90%)	3 (16.70%)	18 (28.10%)
Light	674 (33.40%)	4 (22.20%)	19 (29.70%)
Moderate	435 (21.60%)	1 (5.60%)	8 (12.50%)
Hazardous	224 (11.10%)	4 (22.20%)	8 (12.50%)
Harmful	130 (6.40%)	1 (5.60%)	5 (7.80%)
Past smoker	909 (44.00%)	11 (61.10%)	38 (59.40%)*
Present smoker	192 (9.30%)	0 (0.00%)	7 (10.90%)
Systolic blood pressure, mm Hg	140 ± 18.71	140.89 ± 17.30	140.77 ± 24.08
Diastolic blood pressure, mm Hg	83 ± 10.51	81.08 ± 8.44	81.18 ± 12.09
Forced vital capacity, l	3.11 ± 0.84	2.81 ± 0.65	2.99 ± 0.82
BMI	26.79 ± 4.93	27.35 ± 4.00	28.35 ± 6.84
Physical health self-report (SF-12)	72.36 ± 27.46	72.82 ± 30.09	65.48 ± 29.23*
Mental health self-report (SF-12)	81.49 ± 29.41	78.14 ± 30.60	78.27 ± 29.63
Visual acuity (no. of letters on Snellen chart)	25.86 ± 3.89	25.05 ± 4.58	24.06 ± 5.88

* p < 0.05, ** p < 0.01 compared with normal sample.

Discussion

The main strengths of this study are the investigation of a wide range of health and lifestyle risk factors for MCI in a large and comparatively young community-based cohort of older adults. In addition, predictors of a less specific clinical group, having any MCD, were also investigated because we have previously shown [16] that the any-MCD is more stable than an MCI diagnosis based on consensus criteria. That is, of those diagnosed with MCI or any-MCD, a large proportion (71%) of those diagnosed with MCI reverted to non-MCI status 4 years later, whereas only 11% of any-MCD individuals lost their diagnosis (there were no dementia diagnoses). Consequently, the any-MCD is seen as a clinical category overlapping and sharing many characteristics with MCI. The differences in predictors discussed below are therefore thought to predominantly indicate difference in statistical power af-

Table 2. Health and lifestyle predictors of transition from normal ageing to MCI and any-MCD adjusted for age, sex and education

Predictors	MCI		Any-MCD	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Diabetes	0.73 (0.95–5.52)	0.756	2.06 (0.99–4.28)	0.054
Taking oral diabetes medication	1.30 (0.17–9.96)	0.799	2.87 (1.26–6.53)	0.012
Taking cholesterol-lowering medication	0.88 (0.29–2.70)	0.822	2.01 (1.20–3.37)	0.008
Taking blood pressure medication	1.33 (0.51–3.45)	0.563	1.64 (0.99–2.71)	0.056
Systolic blood pressure, mm Hg	1.00 (0.98–1.03)	0.878	1.00 (0.99–1.02)	0.838
Diastolic blood pressure, mm Hg	0.98 (0.93–1.02)	0.332	0.98 (0.95–1.03)	0.080
Stroke	–	–	2.33 (0.91–6.02)	0.079
Arthritis	1.97 (0.76–5.12)	0.163	1.73 (1.04–2.90)	0.037
FVC, l	0.45 (0.44–0.46)	0.029	0.69 (0.47–1.03)	0.068
BMI	1.01 (0.93–1.10)	0.752	1.05 (1.05–1.09)	0.025
Physical health self-report	1.02 (0.97–1.09)	0.359	0.97 (0.95–0.99)	0.011
Taking anxiety medication	4.08 (1.16–14.39)	0.029	1.76 (0.69–4.51)	0.238
Goldberg anxiety scale	0.98 (0.79–1.21)	0.856	1.04 (0.93–1.15)	0.521
Taking depression medication	4.12 (1.16–14.64)	0.029	3.71 (1.76–7.81)	0.001
Goldberg depression scale	1.19 (0.96–1.46)	0.106	1.15 (1.02–1.29)	0.026
Mental health self-report	0.99 (0.99–1.05)	0.705	1.00 (0.96–1.03)	0.823
Past alcohol intake category (1 = abstainer; 6 = harmful)	0.76 (0.50–1.15)	0.200	0.88 (0.72–1.09)	0.253
Past alcohol intake (quadratic trend)	1.48 (1.13–1.94)	0.005	1.16 (0.97–1.38)	0.097
Abstain to drink alcohol (vs. all others)	9.10 (3.02–27.42)	<0.001	2.23 (0.92–5.39)	0.076
Harmful/hazardous past drinking (vs. all others)	1.76 (0.61–5.14)	0.298	1.15 (0.61–2.17)	0.671
Past smoker	1.88 (0.71–5.02)	0.203	1.78 (1.06–3.00)	0.031
Visual acuity (Snellen)	0.93 (0.86–1.01)	0.073	0.96 (0.91–1.01)	0.139
APOE*E4	0.55 (0.16–1.93)	0.354	0.66 (0.35–1.24)	0.193
APOE*E2	2.45 (0.86–6.93)	0.092	1.31 (0.67–2.54)	0.427

forded by different sample sizes rather than instrumental differences supported by fundamentally different underlying pathological processes.

As predicted, past smoking, and taking anxiety/depression medications were associated with increased risk of MCI and any-MCD in all analyses while alcohol consumption was found to be protective (when not taken in hazardous quantities) after controlling for sex, age, and education. These factors have been identified in previous research investigating conversion to dementia [30], but the fact that they can be reliably detected in a relatively young sample known to be cognitively intact at the start of the study and in relation to MCI and any-MCD, not dementia, is important because it confirms the relevance of MCI as a precursor stage to dementia and suggests a progressive effect of certain risk and protective factors for dementia.

Past smoking, which has been consistently associated with increased risks of developing dementia [see 12 for a review] was associated with a 2–3-fold increase in risk of developing MCI and any-MCD. The mechanisms mediating this effect are not fully understood but include an increased risk of cardiovascular disease in smokers. Recent research in rodents [31] has shown that exposure to cigarette smoke promotes arterial thrombosis and increases arterial wall thickening which are likely to lead to decreased perfusion, increased risk of stroke, and increased blood pressure. White matter hyperintensities, which are thought to reflect small vessel disease, are associated with hypertension and cardiovascular disease and are a risk factor for dementia. An association between smoking and white matter hyperintensities has been demonstrated and is consistent with a cardiovascular effect of smoking on cognition. These findings strengthen the view that smoking is bad for mental health and should be avoided.

Alcohol consumption was assessed using the AUDIT, which has been shown to have good psychometric characteristics in a variety of contexts and cultures [e.g. 32]. The association between alcohol consumption and cognitive impairment was complex and followed both linear and quadratic functions, with abstinence and high intake being associated with increased risk and moderate consumption being associated with decreased risk of both

Table 3. Health and lifestyle predictors of conversion to MCI (full and reduced models)

Models	Full		Reduced	
	Sig.	Exp(B)	Sig.	Exp(B)
Systolic blood pressure, mm Hg	0.360	1.02 (0.98–1.05)		
Diastolic blood pressure, mm Hg	0.128	0.95 (0.88–1.02)		
Arthritis	0.238	1.89 (0.66–5.46)		
FVC, l	0.098	0.52 (0.24–1.13)		
Diabetes	0.563	0.53 (0.06–4.6)		
BMI	0.882	1.01 (0.91–1.11)		
Physical health self-report	0.033	1.08 (1.01–1.15)		
Mental health self-report	0.309	1.05 (0.95–1.16)		
Visual acuity (Snellen)	0.051	0.92 (0.84–1)	0.059	0.92 (0.85–1.00)
Taking blood pressure medication	0.547	1.41 (0.46–4.3)		
Taking anxiety medication	0.317	2.6 (0.4–16.9)	0.056	3.58 (0.97–13.22)
Taking depression medication	0.314	2.79 (0.38–20.57)		
Taking cholesterol-lowering medication	0.436	0.6 (0.16–2.18)		
Goldberg anxiety scale	0.293	0.83 (0.58–1.18)		
Goldberg depression scale	0.021	1.54 (1.07–2.22)		
Past smoker	0.050	3.26 (1–10.67)	0.041	3.22 (1.05–9.87)
Past alcohol intake category	0.031	0.58 (0.36–0.95)	0.021	0.59 (0.37–0.92)
Past alcohol intake category (quadratic)	0.009	1.52 (1.11–2.08)	0.002	1.58 (1.18–2.11)
APOE*E4	0.458	0.61 (0.16–2.26)		
APOE*E2	0.089	2.67 (0.86–8.27)	0.063	2.74 (0.95–7.97)
Model fit	R^2	−2 Log likelihood	R^2	−2 Log likelihood
	0.218	163.52	0.130	181.20

All models are adjusted for age, sex, and education.

MCI and any-MCD. This is consistent with previous research showing that moderate alcohol consumption is protective of dementia [33] and with cross-sectional findings of the PATH study showing an inverse U-association between drinks per week and cognitive performance [34].

Depression and anxiety are known risk factors for dementia, but it remains unclear whether they occur in the prodrome to dementia or are causally related. Recently, Palmer et al. [30] showed that individuals with both MCI and anxiety symptoms were more than 13 times more likely to develop AD than cognitively intact individuals and twice as likely compared to individual with MCI without anxiety symptoms [30]. In the present study, participants taking anxiety or depression medication had a 4-fold increase in risk of developing MCI or any-MCD. Self-reported anxiety or depression, however, was not or only mildly predictive.

Cardiovascular measures were significant predictors of transition to any-MCD, however, they followed an unexpected pattern. It may be the results were partly due to error in measurement as blood pressure was only measured twice in the same setting on a single occasion. However, correlations of these measures between the first and second wave of measurement 4 years later were greater than 0.5 which suggests that substantial, stable variance was indexed by these measures. Blood pressure medication and higher systolic measures were associated with an increased risk, whereas higher diastolic measures were associated with a decreased risk of any-MCD. These findings partly contradict previous findings showing (1) a decreased risk of cognitive decline [35] and a milder occurrence of Alzheimer pathology [36] in individuals taking anti-hypertensive medication, and (2) an increased risk of developing dementia in hypertensive individuals [37], and should be interpreted cautiously. However, a Cochrane review [38] found no evidence of association between blood pressure-lowering treatments and the risk of developing dementia or cognitive impairment and we have not found studies reporting a risk associated with heightened diastolic blood pressure when other relevant variables were controlled. In addition, in the oldest-old,

Table 4. Health and lifestyle predictors of conversion to any-MCD (full and reduced models)

Models	Full		Reduced	
	Sig.	Exp(B)	Sig.	Exp(B)
Systolic blood pressure, mm Hg	0.154	1.01 (0.99–1.03)	0.057	1.02 (1.00–1.04)
Diastolic blood pressure, mm Hg	0.022	0.96 (0.93–0.99)	0.011	0.96 (0.92–0.99)
Arthritis	0.253	1.39 (0.79–2.44)		
FVC, l	0.484	0.86 (0.56–1.31)		
Diabetes	0.842	1.09 (0.48–2.44)		
BMI	0.255	1.03 (0.98–1.07)	0.054	1.04 (1.00–1.08)
Physical health self-report	0.892	1 (0.97–1.03)		
Mental health self-report	0.380	1.02 (0.97–1.07)		
Visual acuity (Snellen)	0.189	0.96 (0.91–1.02)		
Taking blood pressure medication	0.423	1.26 (0.72–2.2)		
Taking anxiety medication	0.526	0.67 (0.2–2.28)		
Taking depression medication	0.010	3.66 (1.36–9.81)	0.003	3.25 (1.51–7.00)
Taking cholesterol-lowering medication	0.208	1.45 (0.81–2.57)		
Goldberg anxiety scale	0.416	0.93 (0.79–1.1)		
Goldberg depression scale	0.126	1.16 (0.96–1.4)		
Past smoker	0.023	1.94 (1.1–3.42)	0.018	1.97 (1.12–3.44)
Past alcohol intake category	0.080	0.77 (0.58–1.03)	0.046	0.75 (0.57–1.00)
Past alcohol intake category (quadratic)	0.166	1.14 (0.95–1.37)	0.087	1.17 (0.98–1.40)
APOE*E4	0.191	0.64 (0.33–1.24)		
APOE*E2	0.272	1.47 (0.74–2.92)		
Model fit	R^2	–2 Log likelihood	R^2	–2 Log likelihood
	0.105	518.55	0.075	533.66

All models are adjusted for age, sex, and education.

it was found that higher systolic blood pressure was associated with better cognition [39] and in another longitudinal study investigating the relationship between blood pressure and late-life cognitive change, no linear association was found between systolic or diastolic blood pressure and cognition but a curvilinear relationship between diastolic blood pressure and cognition was present, showing an association between both high and low diastolic blood pressure and decreased cognition [40]. It may be that blood pressure medication and/or lower diastolic blood pressure in some individuals lead to chronic cerebral hypoperfusion/hypoxia [41] which over time might lead to neurodegeneration and negatively impact on cognition. These associations should be investigated further in future studies since, if they can be replicated, interventions focusing on low as well as high blood pressure management might be initiated to decrease the risk of cognitive decline in hypertensive individuals.

BMI, cholesterol-lowering medication, systolic blood pressure, diabetes, and diabetes medication were all found to be predictors of any-MCD. These findings are consistent with past research showing an association between the metabolic syndrome, cardiovascular disease, cognitive impairment, and dementia. However, while cognitive impairment was associated with greater BMI, higher systolic blood pressure, and having diabetes as expected, it was somewhat surprisingly positively associated with taking cholesterol-lowering medication and diabetes medication. Because these medications reduce the level of known risk factors (hypercholesterolemia and hyperglycemia), they could have been expected to be associated with decreased rather than increased cognitive impairment. In one clinical trial assessing anti-inflammatory drugs, participants who elected to use cholesterol medication had a lower risk of developing AD [42]. However, in large prospective epidemiological studies, cholesterol-lowering drugs were not found to be protective or a risk for AD [43]. The present findings are therefore likely to indicate that those individuals prescribed cholesterol-lowering medication are at higher risk due to other factors such as the pathological processes associated with high blood cholesterol prior to treatment. It may also be

that if the cholesterol-lowering medication has been instituted relatively recently, it serves as a marker of disease without having had time to affect the course of neuropathological processes. It would therefore be preferable if information on the length of treatment be collected and included in the analyses of future studies of this kind.

Some variables emerged as potential predictors of conversion in univariate analyses but did not remain significant in multivariate analyses. They should be considered exploratory, and further follow-up is required to reveal whether their significance is reliable. For MCI, increased FVC, which may act as a proxy of physical and cardiovascular fitness, was associated with decreased risk of MCI and has been associated with better cognitive performance [44] and fewer white matter hyperintensities in the same study.

A previous study [3] investigating the predictors of MCI and AD in a larger and older cohort with substantially greater MCI prevalence found sex differences that were investigated in a stratified analysis. The number of converters in the present study did not provide a sufficient statistical power for such an analysis, but, although less sensitive, none of the sex interactions reached significance in the present study.

This study had a number of limitations. Beside those discussed above, many of the measures were based on self-report and are therefore open to bias. The FVC was based on 2 successive measures during the same session and may not be very reliable, although, as for the blood pressure measurements, correlations between the measures used in the present study and those collected in the second wave of measurement were high (r > 0.8). A relatively small number of participants converted to MCI and therefore some of the cells used for analysis were small. However, a number of risk factors for MCI were shared with any-MCD, which affected more participants, sug-gesting that the present findings are unlikely to be artefacts. It is also possible that some of these findings are underestimates, since the studied individuals were located in an affluent, well-educated city and probably engage in a healthier lifestyle with better dietary habits and lower smoking rates than the rest of the population (56% of participants ever smoked compared with 60% in the Australian population). Finally, despite the significance of these results in the assessment of population-based risks, they do not explain a sufficiently large proportion of the variance in clinical status to enable the classification of single individuals. Despite these limitations, theoretically relevant risk and protective factors were identified.

These findings indicate that lifestyle factors, and specifically smoking and alcohol consumption, are particularly important predictors of cognitive impairments in ageing populations and should be the focus of renewed interventions. These results also have clinical relevance, since as found in AD [30], anxiety and depression symptoms appear to be associated with a substantially greater risk of MCI. Finally, the possibility that blood pressure medications and low diastolic blood pressure might be associated with a greater risk of cognitive impairment should be further investigated.

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