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# Associations Between Lifestyle and Cognitive Function Over Time in Women Aged 40–79 Years

Ada H.Y. Lo[a,1], Richard J. Woodman[b,*,1], Nancy A. Pachana[a], Gerard J. Byrne[c] and Perminder S. Sachdev[d]
[a]*School of Psychology, University of Queensland, St Lucia, Queensland, Australia*
[b]*Flinders Centre for Epidemiology and Biostatistics, School of Medicine, Flinders University, South Australia, Australia*
[c]*School of Medicine, University of Queensland, and Royal Brisbane and Women's Hospital, Brisbane, Australia*
[d]*Brain and Ageing Research Program, School of Psychiatry, University of New South Wales, and Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia*

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**Abstract**.
**Background:** Smoking, excessive drinking, and physical inactivity are associated with reduced cognitive function but the independence, domain specific cognitive effects, and trajectories of these associations are not firmly established.
**Objective:** Our aim was to examine these lifestyle-cognitive function associations in middle-to-older aged women across time.
**Methods:** Cohort study design with repeat surveys (2001, 2005, and 2008). Participants were volunteers from a random sample of Australian women on the Brisbane electoral roll; mean (±SD) age 60 ± 11 years in 2001. Outcome measures were the Mini-Mental State Examination (MMSE), Auditory Delayed Index (ADI), Visual Delayed Index (VDI), Working Memory Index (WMI), and Processing Speed Index (PSI).
**Results:** 489 women completed cognitive testing in 2001, 451 in 2005, and 376 in 2008. Mean (±SD) cognitive scores in 2001 were MMSE: 29.1 ± 1.2, ADI: 104.6 ± 13.4, VDI: 107.2 ± 14.0, WMI: 104.1 ± 12.3, and PSI: 102.7 ± 11.8. Multivariate adjusted mean scores (95% CI) over the 7-year study period were higher for moderate drinkers than non-drinkers for the MMSE (β = 0.32; 0.04, 0.61), the VDI (β = 4.33; 0.96, 7.70), and the WMI (β = 3.21; 0.34,6.07). Current smokers performed worse than never-smokers for the MMSE (β = −0.35; 0.64, −0.06), the VDI (β = −3.91; −7.57, −0.26), the WMI (β = −3.42; −6.67, −0.18), and the PSI (β = −5.89; −8.91, −2.87). PSI was higher in women performing strenuous physical activity compared to inactive women (β = 2.14; 0.37, 3.90). None of the three lifestyle parameters influenced the changes in cognition across time.
**Conclusions:** Alcohol and exercise were associated with selective protective effects and tobacco with selective harmful effects on cognitive function in middle-to-older aged women. Associations remained consistent across time.

Keywords: Cognitive function, drinking, physical activity smoking, women

## INTRODUCTION

Smoking, excessive drinking, and physical inactivity are well-established risk factors for cardiovascular disease that have also been implicated in cognitive decline, a process that begins in middle age [1] and may affect women more than men [2]. However, in

[1]These authors contributed equally to the manuscript.

*Correspondence to: Richard J. Woodman, Director, Flinders Centre for Epidemiology and Biostatistics (FCEB), Discipline of General Practice, Flinders University, GPO Box 2100 Adelaide, SA 5001, Australia. Tel.: +61 08 7221 8537; Fax: +61 08 7221 8544; E-mail: Richard.Woodman@flinders.edu.au.

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addition to the limitations of previous lifestyle and cognitive function association studies, important research questions still remain. Whether the associations are global in nature or whether they differentially impact specific cognitive functions such as psychomotor speed [3] is unclear. While a protective effect of alcohol may exist in men, drinking may be harmful for women [4, 5] even in moderation [6]. Similarly, although current smoking is a significant risk factor for cognitive decline [7], recent results from the Whitehall II study suggested this association is apparent in men but not women [8], although previous prospective studies with older women have observed cognitive decline in smokers [5]. Physical activity may protect against cognitive decline among women [2, 9–11] even if only started later in life [11], but the benefits of exercise may not occur across all cognitive areas [10] and may depend upon exercise intensity [9].

In addition to conflicting results between men and women, many of the studies assessing cognitive function and lifestyle have not assessed the independent effects of all three lifestyle factors together [8, 9, 12], or have not adjusted for important confounders including socio-demographic status [2], measures of health such as obesity and metabolic abnormalities [13], or potential effect modifiers, such as the genetic risk of dementia determined by apolipoproteinE-$\varepsilon$4 allele (ApoE-$\varepsilon$4) presence which may [12] or may not [14] have negative effects for drinking and protective effects for smoking [15]. Additionally, most studies have been either cross-sectional [16] or had relatively short follow-up periods [9, 14, 17].

Given these continuing debates, we present data from a longitudinal cohort of Australian women to clarify the independent relationships of lifestyle behaviors with cognitive function in middle-to-older aged women over a seven year period. With measurements at 3 time-points and detailed information available for each lifestyle variable as well as a wide range of clinical and socio-demographic data, we hypothesized that we would observe independent cognitive function versus lifestyle associations, that these associations may be dose or intensity related, and that they may also increase in strength across time.

## METHODS

### *Study population*

Data were collected for the LAW study, which commenced in 2001 and has been previously described [18]. Briefly, the LAW study is a population-based study of urban women, aged 40–79 years at cohort entry and living in Brisbane in the State of Queensland, Australia. An age-stratified simple random sample of 40–79 year-olds was selected for potential participation using the year 2000 North Brisbane Health District Electoral Roll. A total of 1,598 women were invited to participate, with a 68% response rate ($n = 1{,}082$). Eligibility was restricted to women who were ambulatory or willing to be transported, able to commute to the Royal Brisbane and Women's Hospital (RBWH) to undergo several clinical assessments per year, and willing to provide informed consent. Together, this resulted in an age-stratified sample of 511 women being recruited in 2001, with approximately 120 women in each of four 10-year age strata (40–49 years, $n = 125$; 50–59 years, $n = 128$; 60–69 years, $n = 128$; and 70–79 years, $n = 130$). Compared to those who did not participate, the women were younger ($59.8 \pm 10.9$ years versus 64.7 years $\pm$ 12.2 years, $p < 0.0001$) and relatively fewer were engaged in home duties or were retired (29.5% versus 70.5%, $p < 0.001$) [18]. Ethics approval for the study was granted by the human research ethics committees of the RBWH and the University of Queensland. The study was conducted in accord with the Helsinki Declaration of 1975.

### *Procedures*

Participants were assessed at RBWH in 2001 (Phase 1), 2005 (Phase 2), and 2008/2009 (Phase 3). Data on socio-demographic factors, health status, and medical history were obtained through clinical interview with research team members who were trained clinical psychologists and blood was obtained for glucose, cholesterol, triglycerides, and hormones. Clinical characteristics collected at each survey were seated clinic blood pressure, body mass index (BMI), menopausal status (yes/no), hypertension (yes/no), and dyslipidemia (yes/no) based on current medication and lipids. Information on genotyping for ApoE- $\varepsilon$4 risk (yes/no for the presence or absence of at least one copy of the $\varepsilon$4 allele) was collected in 2001. Presence of psychological distress over the past month was assessed each year using clinical interview and the 30-item version of the General Health Questionnaire (GHQ-30) [19]. The two-point absent or present score was used for each item with a total score of five used to identify psychological distress [20]. Socio-demographic variables measured included age, marital status (never married/married or defacto/divorced or separated/widowed), socioeconomic status using employment status (home duties/casual paid or unpaid/

full-time/part-time/unemployed or student/retired/disabled/other), and education (no qualifications/secondary school year 10 or apprenticeship/secondary school year 12/post-secondary education).

*Cognitive measures*

The Wechsler Memory Scale Third Edition (WMS-III) [21] is a standardized individually administered battery of tests that evaluates visual and auditory learning and memory functions in adults, aged 16–89 years. From the six primary subtests, three memory indices were derived; the Auditory Delayed Index (ADI), Visual Delayed Index (VDI), and Working Memory Index (WMI), chosen to represent verbal, visual, and working memory, respectively. Two subtests from the Wechsler Adult Intelligence Scale (WAIS-III) [22] were included to generate the Processing Speed Index (PSI). Each of the four index scores are age-standardized to the US population and have a mean ($\pm$SD) of $100 \pm 15$, and test-re-test reliabilities of 0.76 to 0.84 [22]. The MMSE assesses global cognitive functioning [23] with scores ranging from 0 to 30.

*Lifestyle measures*

Smoking status, alcohol use, and level of physical activity were assessed at each phase. Participants indicated if they were non-smokers, current smokers, or smokers within the past 12 months. The number of standard drinks (10 g alcohol) per week within the past 12 months was calculated using the Alcohol Use Disorders Identification Test (AUDIT) [24]. Individuals were classified into five categories using national guidelines [25]: non-drinkers, occasional (<1 standard drink/week); light (1–7 drinks/week); moderate (8–14 drinks/week); and heavy (>14 drinks/week). Level of physical activity within the past 12 months was assessed in 2001 and 2005 using a 6-point scale (1 = moving only for necessary chores to 6 = heavy exercise/competitive sport several times/week) [26] and in 2008 using a 4-point scale (inactive/light/moderate/strenuous activity). To compare physical activity over time, the 6 point scale from 2001/2005 was recoded as 1 = inactive, 2/3 = light, 4 = moderate, and 5/6 = strenuous.

*Statistical analysis*

Lifestyle effects on each cognitive measure were assessed using linear mixed-effects regression models with STATA (version 11.1, StataCorp Inc., Texas). Participants were treated as a random effect and smoking, drinking, physical activity, survey year (all as categorical covariates) and age at baseline (continuous) were treated as fixed effects (model 1). Additional adjustment was performed for socioeconomic status (education, marital, and employment status), menopausal status, ApoE-$\varepsilon$4 genotype, BMI, hypertension, dyslipidemia, diabetes (defined as a fasting glucose in 2001 equal to or greater than 7 mmol/l), and psychological distress (yes/no) (model 2). To assess the effects of changes across time, we included a global time x lifestyle behavior interaction term. We also assessed the significance of ApoE-$\varepsilon$4 x lifestyle behavior interaction terms. A test of global effects and linear trend were performed for each lifestyle behavior using 2-sided $p$-values with significance at $p < 0.05$. Linear trends were assessed by replacing categorical variables with a single continuous variable. In random-intercept models in which the independent variables vary both within-subject (i.e., across time) and between-subjects, the regression coefficients are a weighted average of between-subject and within-subject effects. Therefore, in a sensitivity analysis we formally compared these two effects for each lifestyle factor [27]. If one of these two estimators was significant and the other non-significant we compared the difference in the two using a Wald test. Each of the main analyses were performed on a modified intention-to-treat principle; for cases in which some values were missing, we assumed that the data were missing at random (MAR) since those that completed all three phases of the cognitive testing were little different in terms of drinking, smoking, and physical activity to those who did not. To further verify our assumption of MAR, we conducted a sensitivity analysis using complete cases only ($n = 363$) to assess whether the effects were similar.

## RESULTS

*Participants*

Of the initial 511 women enrolled into the study, 22 did not complete baseline cognitive testing due to severe sensory impairment ($n = 4$), inadequate proficiency in English ($n = 6$), withdrawal ($n = 11$), or death (1) and were not included in the analysis. As only six women reported greater than 14 standard drinks per week at baseline, these subjects were combined with moderate drinkers. Of the 489 participants who completed baseline cognitive testing in 2001, 451 participated in cognitive testing in 2005 and 376 in 2008. The mean $\pm$ SD follow-up time was $6.35 \pm 2.20$ years

(range 0.00–8.19). Compared to women in the general Australian population of the same age group (55–64 years) [28], women in this study were less likely to be current smokers (9% versus 16%, $p < 0.001$), less likely to be non-drinkers (19% versus <40%, $p < 0.001$), less likely to be moderate/heavy drinkers (11% versus 16%, $p = 0.003$), and less likely to be overweight/obese (56% versus 65%, $p < 0.001$). More participants were classified as performing light activity than females of the same age in the Queensland population who walk for exercise (69.0% versus 45.7%, $p < 0.001$) [29].

*Subject characteristics*

The mean ± SD age of the 489 subjects was 60.0 ± 11.0 years. The mean ± SD age at baseline of subjects who participated in 2001 alone was 66.1 ± 12.1 years, of those who participated in 2001 and 2005 was 63.2 ± 10.7 years and of those who participated in all 3 surveys was 58.7 ± 10.4 years ($p < 0.001$). Table 1 describes the characteristics of the participants at baseline. In unadjusted analysis, non-smokers had higher PSI than smokers ($p = 0.03$), those that drank alcohol had higher VDI than non-drinkers ($p = 0.02$), and women that were physically active had higher MMSE scores and higher PSI scores ($p < 0.001$) than those who were inactive ($p = 0.04$). Table 2 describes the percentage of women within each lifestyle category over time.

*Associations between lifestyle factors at baseline*

When comparing associations between lifestyle variables at baseline, there was a strong association between smoking status and drinking status with those that currently smoked less likely than those that had never smoked to be non-drinkers (4.4% versus 23.3%) and more likely to be moderate or heavy drinkers (22.2% versus 5.0%) ($\chi^2 = 30.4$; 6df, $p < 0.001$). There was no significant association between smoking status and level of physical activity ($\chi^2 = 11.7$; 6df, $p = 0.07$) and no significant association between level of physical activity and drinking status ($\chi^2 = 15.05$; 9df, $p = 0.09$).

*Cognitive function*

The overall raw mean (±SD) scores at baseline for the cognitive function tests were 29.1 ± 1.2 for the MMSE, 104.6 ± 13.4 for the ADI, 107.2 ± 14.0 for the VDI, 104.1 ± 12.3 for the WMI, and 102.7 ± 11.8 for the PSI. Table 3 presents the estimated marginal effects of alcohol, smoking, and physical activity, and Fig. 1 displays the adjusted marginal means for each cognitive outcome and lifestyle activity.

*1. Association between cognitive function and age*

Older age was associated with a lower MMSE score and this effect remained after adjustment for age related factors including the presence of hypertension and dyslipidemia ($\beta = -0.44$ per 10 years, 95% CI = −0.58, −0.31; $p < 0.001$ for linear trend). None of the age standardized outcomes (ADI, VDI, WMI, and PSI) were related to age after adjustment for age related variables.

*2. Association between cognitive function and time*

The marginal mean MMSE score in 2001 was 29.1 ± 0.1 and declined in 2005 and 2008 (29.0 ± 0.1 and 28.8 ± 0.1, respectively, $p < 0.001$ for linear trend). The ADI increased across time (104.6 ± 0.6, 108.2 ± 0.6, 113.1 ± 0.7, $p < 0.001$ for linear trend) suggesting a learning effect in participants. The marginal mean VDI score in 2001 was 107.3 ± 0.7 and increased in 2005 and 2008 (111.3 ± 0.7 and 117.8 ± 0.7, respectively, $p < 0.001$ for linear trend). The marginal mean WMI score in 2001 was 104.2 ± 0.6, remained similar in 2005 (103.3 ± 0.6), but was higher in 2008 (108.0 ± 0.6, $p < 0.001$). The marginal mean PSI score in 2001 was 102.7 ± 0.6 and increased in both 2005 (107.5 ± 0.6, $p < 0.001$) and 2008 (108.3 ± 0.6, $p < 0.001$).

*3. Association between cognitive function and smoking*

The MMSE score was lower in current smokers compared to never smokers ($p = 0.02$) but not different between previous smokers and never smokers ($p = 0.59$). The VDI was lower in current smokers compared to never smokers ($p = 0.03$). Previous smokers ($p = 0.01$) and current smokers ($p = 0.04$) both performed worse than never-smokers for the WMI ($p = 0.007$ for linear trend). Current smokers and previous smokers performed worse than never-smokers for the PSI ($p < 0.001$ and $p = 0.04$, respectively, and $p < 0.001$ for linear trend). The effects of current smoking compared to never smoking for PSI was limited to a between subject effect ($\beta = -8.2$, 95% CI = −12.5, −3.9; $p < 0.001$) rather than a within-subject effect ($\beta = -1.2$, 95% CI = −6.0,3.7; $p = 0.64$). The difference between these two effects was significantly different ($\beta = -7.02$, 95% CI = −13.6, −0.5; p-0.04).

*4. Association between cognitive function and drinking*

Moderate drinkers had higher MMSE scores than non-drinkers ($p = 0.03$ and $p = 0.01$ for linear trend), higher VDI scores than non-drinkers ($p = 0.01$;

Table 1
Participants' characteristics at phase 1 (2001) according to smoking, drinking and activity status ($n = 489$)[7]

| | Non-smoker ($n = 262$) | Current/ Ex-smoker ($n = 218$) | $p$-value[5] | Non-drinker ($n = 93$) | Drinker ($n = 384$) | $p$-value[5] | Active ($n = 110$) | Inactive ($n = 364$) | $p$-value[5] |
|---|---|---|---|---|---|---|---|---|---|
| Age, y (mean ± SD)[1] | 61.5 ± 10.5 | 58.2 ± 11.0 | $p = 0.001$ | 64.3 ± 9.7 | 58.8 ± 10.8 | $P < 0.001$ | 54.9 ± 9.3 | 61.6 ± 10.8 | $p < 0.001$ |
| BMI, kg/m$^2$ (mean ± SD) | 26.6 ± 5.3 | 26.3 ± 5.2 | $p = 0.57$ | 27.6 ± 5.9 | 26.2 ± 5.0 | $p = 0.02$ | 24.6 ± 4.4 | 27.1 ± 5.3 | $p < 0.001$ |
| Education | | | | | | | | | |
| No qualifications, n(%) | 30 (12) | 22 (10) | | 14 (15) | 38 (10) | | 7 (6) | 45 (12) | |
| Year 10[2] or apprenticeship, n(%) | 142 (55) | 110 (51) | $p = 0.008$ | 58 (63) | 191 (50) | $p = 0.62$ | 46 (42) | 201 (55) | $p < 0.001$ |
| Year 12[2], n(%) | 48 (18) | 43 (20) | | 13 (14) | 79 (21) | | 23 (21) | 67 (19) | |
| Post high school education, n(%) | 40 (15) | 42 (19) | | 7 (8) | 74 (19) | | 34 (31) | 48 (13) | |
| Menopausal | | | | | | | | | |
| No, n(%) | 54 (21.5) | 64 (30.2) | $p = 0.03$ | 14 (15.4) | 104 (28.1) | $p = 0.01$ | 43 (40.2) | 72 (20.6) | $p < 0.001$ |
| Yes, n(%) | 197 (78.5) | 148 (69.8) | | 77 (84.6) | 266 (71.9) | | 64 (59.8) | 278 (79.4) | |
| ApoE risk | | | | | | | | | |
| At risk[a] | 181 (69.1) | 159 (73.3) | | 68 (73.1) | 271 (70.8) | | 78 (70.9) | 259 (71.4) | |
| No risk[b] | 76 (29.0) | 55 (25.3) | $p = 0.59$ | 25 (26.9) | 105 (27.4) | $p = 0.41$ | 30 (27.3) | 98 (27.0) | $p = 0.99$ |
| Both ApoE4 & ApoE2/E3 alleles | 5 (1.9) | 3 (1.4) | | 0 (0.0) | 7 (1.8) | | 2 (1.8) | 6 (1.7) | |
| Hypertension[3] | | | | | | | | | |
| No, n(%) | 126 (48.1) | 136 (62.4) | $p = 0.002$ | 35 (37.6) | 226 (58.9) | $p < 0.001$ | 74 (67.3) | 186 (51.1) | $p = 0.003$ |
| Yes, n(%) | 136 (51.9) | 82 (37.6) | | 58 (62.4) | 158 (41.2) | | 36 (32.7) | 178 (48.9) | |
| Dyslipidaemia[3] | | | | | | | | | |
| No, n(%) | 101 (38.9) | 112 (51.4) | $p = 0.005$ | 37 (39.8) | 177 (46.1) | $p = 0.27$ | 60 (54.6) | 151 (41.5) | $p = 0.02$ |
| Yes, n(%) | 161 (61.5) | 106 (48.6) | | 56 (60.2) | 207 (53.9) | | 50 (45.5) | 213 (58.5) | |
| Diabetes[4] | | | | | | | | | |
| No, n(%) | 250 (95.4) | 212 (97.2) | $p = 0.29$ | 86 (92.5) | 373 (97.1) | $p = 0.03$ | 107 (97.3) | 349 (95.9) | $p = 0.50$ |
| Yes, n(%) | 12 (4.6) | 6 (2.8) | | 7 (7.5) | 11 (2.9) | | 3 (2.7) | 15 (4.1) | |
| Psychological distress[5] | | | | | | | | | |
| No, n(%) | 193 (73.7) | 136 (62.4) | $p = 0.008$ | 69 (74.2) | 258 (67.2) | $p = 0.19$ | 82 (74.6) | 244 (67.0) | $p = 0.14$ |
| Yes, n(%) | 69 (26.3) | 82 (37.6) | | 24 (25.8) | 126 (32.8) | | 28 (25.5) | 120 (33.0) | |
| Marital Status | | | | | | | | | |
| Never married | 11 (4.2) | 6 (2.8) | | 2 (2.1) | 15 (3.9) | | 4 (3.6) | 13 (3.6) | |
| Married or de-facto relationship | 180 (68.7) | 155 (71.1) | | 62 (66.7) | 270 (70.3) | $p = 0.59$ | 84 (76.4) | 246 (67.6) | $p = 0.24$ |
| Divorced or separated | 34 (13.0) | 29 (13.3) | $p = 0.81$ | 13 (14.0) | 50 (13.0) | | 13 (11.8) | 50 (13.7) | |
| Widowed | 37 (14.1) | 28 (12.8) | | 16 (17.2) | 49 (12.8) | | 9 (8.2) | 55 (15.1) | |
| Employment Status | | | | | | | | | |
| Home duties | 56 (21.4) | 36 (16.6) | | 27 (29.0) | 64 (16.7) | | 16 (14.6) | 76 (20.9) | |
| Casual paid or unpaid | 17 (6.5) | 14 (6.5) | | 5 (5.4) | 26 (6.8) | | 10 (9.1) | 20 (5.5) | |
| Full time | 49 (18.7) | 64 (29.5) | p = 0.03 | 13 (14.0) | 99 (25.9) | p = 0.001 | 34 (30.9) | 78 (21.5) | $p = 0.045$ |
| Part-time | 36 (13.7) | 39 (18.0) | | 7 (7.5) | 68 (17.8) | | 21 (19.1) | 51 (14.0) | |
| Retired | 97 (37.0) | 58 (26.7) | | 40 (43.0) | 114 (29.8) | | 27 (24.6) | 127 (35.0) | |
| Other/disabled/ unemployed/student | 7 (2.7) | 6 (2.8) | | 1 (1.0) | 12 (3.1) | | 2 (1.8) | 11 (3.0) | |
| Baseline cognitive function (2001) | | | | | | | | | |
| MMSE (mean ± SD) | 29.1 ± 1.2 | 29.1 ± 1.2 | $p = 0.78$ | 28.9 ± 1.2 | 29.1 ± 1.2 | $p = 0.06$ | 29.3 ± 1.0 | 29.1 ± 1.2 | $p = 0.04$ |
| (range) | (25–30) | (25–30) | | (25–30) | (25–30) | | (25–30) | (25–30) | |
| ADI (mean ± SD) | 104.6 ± 13.5 | 104.8 ± 13.5 | | 102.6 ± 14.5 | 105.2 ± 13.1 | | 105.4 ± 12.1 | 104.4 ± 13.9 | $p = 0.50$ |
| (range) | (71–140) | (71–136) | $p = 0.87$ | (71–136) | (71–140) | $p = 0.10$ | (71–128) | (71–140) | |
| VDI (mean ± SD) | 106.3 ± 13.5 | 108.5 ± 14.3 | | 104.5 ± 15.0 | 108.1 ± 13.6 | | 108.7 ± 13.7 | 106.7 ± 4.0 | |
| (range) | (72–136) | (72–152) | $p = 0.08$ | (75–140) | (72–152) | $p = 0.02$ | (72–144) | (72–152) | $p = 0.18$ |
| WMI (mean ± SD) | 105.1 ± 11.8 | 103.1 ± 12.7 | | 102.7 ± 12.2 | 104.4 ± 12.3 | | 105.4 ± 11.4 | 103.8 ± 12.6 | |
| (range) | (71–141) | (79–155) | $p = 0.08$ | (71–131) | (81–155) | $p = 0.23$ | (81–136) | (71–155) | $p = 0.22$ |
| PSI (mean ± SD) | 103.8 ± 11.9 | 101.5 ± 11.5 | | 102.5 ± 12.2 | 102.8 ± 11.8 | | 106.7 ± 11.5 | 101.6 ± 11.7 | |
| (range) | (79–150) | (71–137) | $p = 0.03$ | (76–128) | (71–150) | $p = 0.84$ | (79–140) | (79–150) | $p < 0.001$ |

[1]Age when baseline (2001) cognitive tests were performed.[2] Completed at high school; [a]Apo E4 alleles (3/4;4/4); [b]Apo E2 or E3 alleles (3/3;2/3;2/2). [3]Based on current medication and lipid readings. [4]Based on a fasting glucose of 7 mmol/l or above in 2001. [5]Evidence of psychological distress over the past month based on items from the General Health Questionnaire (GHQ-30) and clinical interview [19]. [6]Using $t$-test or Exact test. [7]Missing data were present for smoking status ($n = 9$), drinking status ($n = 12$), and level of physical activity ($n = 15$).

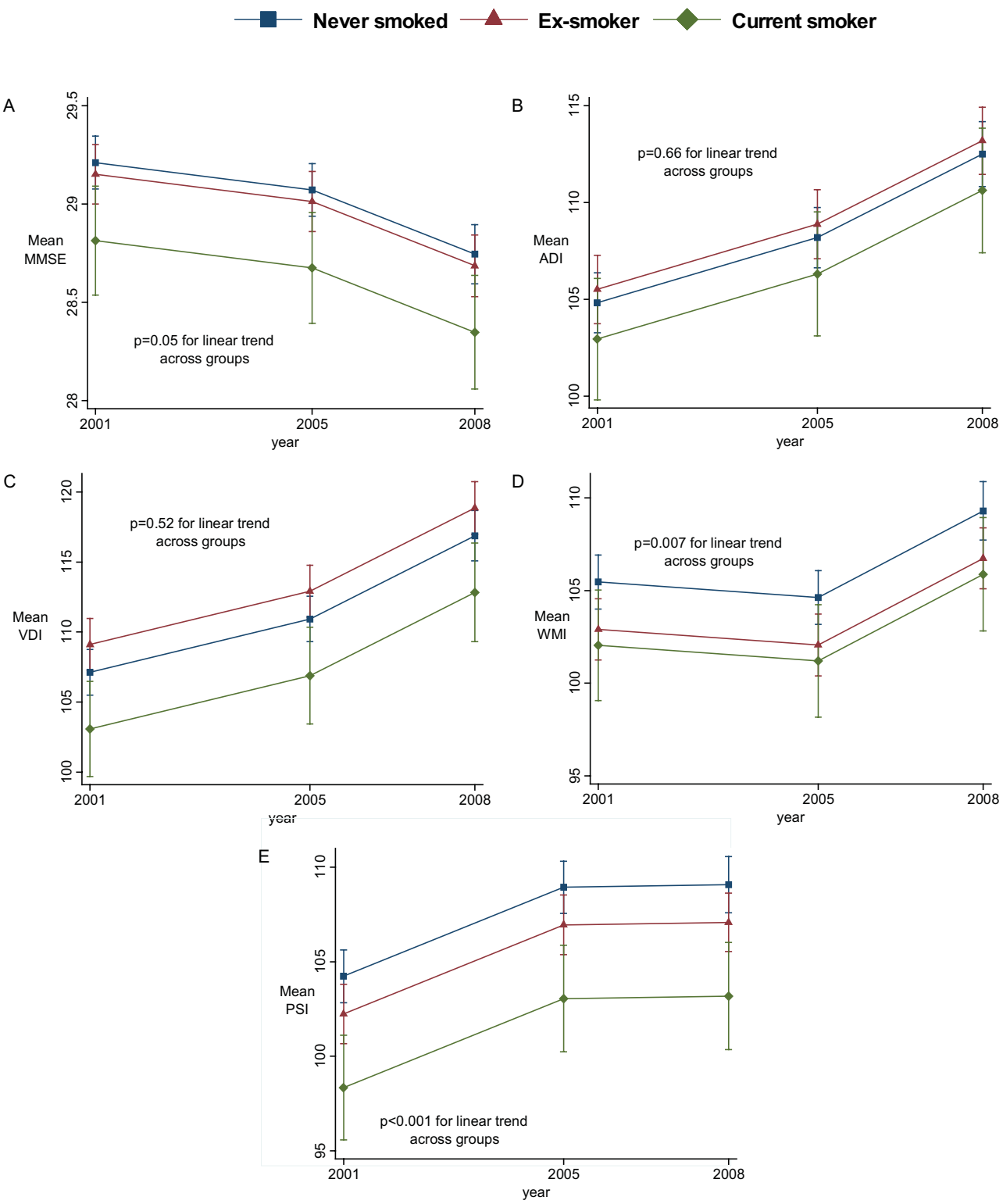


Fig. 1. Adjusted predicted mean (95% CI) cognitive scores from 2001 to 2008 according to smoking status ($n = 489$); obtained from mixed-effects linear regression; adjusted for lifestyle factors (smoking, drinking, and physical activity), age, survey year, BMI, level of education, menopausal status, ApoE risk, hypertension, dyslipidemia, diabetes, recent psychological distress, marital status, and employment status.

Table 2
Distribution of participants at each survey according to alcohol intake, smoking status and level of physical activity

| | 2001 ($n = 489$) | 2005 ($n = 451$) | 2008 ($n = 376$) | 2005 versus 2001 ($p$-value)[1] | 2008 versus 2001 ($p$-value)[2] |
|---|---|---|---|---|---|
| Alcohol | | | | | |
| Non-drinker, n(%) | 93 (19) | 81 (18) | 85 (23) | $\chi^2 = 11.3$, 6df | $\chi^2 = 15.6$, 6df |
| Occasional drinker, n(%) | 105 (22) | 90 (20) | 55 (15) | ($p = 0.08$) | ($p = 0.02$) |
| Light drinker, n(%) | 227 (48) | 223 (50) | 189 (51) | | |
| Moderate/Heavy drinker, n(%) | 52 (11) | 54 (12) | 41 (11) | | |
| Smoking | | | | | |
| Never smoked, n(%) | 262 (55) | 246 (55) | 183 (49) | $\chi^2 = 4.6$, 3df | $\chi^2 = 26.0$, 2df |
| Previous smoker, n(%) | 173 (36) | 158 (36) | 160 (43) | ($p = 0.20$) | ($p < 0.001$) |
| Current smoker, n(%) | 45 (9) | 40 (9) | 27 (7) | | |
| Physical activity | | | | | |
| Inactive, n(%) | 37 (8) | 109 (25) | 47 (13) | $\chi^2 = 61.0$, 6df | $\chi^2 = 45.7$, 6df |
| Light activity, n(%) | 327 (69) | 229 (51) | 168 (46) | ($p < 0.0001$) | ($p = <0.0001$) |
| Moderate activity, n(%) | 38 (8) | 35 (8) | 55 (15) | | |
| Strenuous activity, n(%) | 72 (15) | 72 (16) | 97 (26) | | |

[1]2001 versus 2005, McNemar's test. [2]2001 versus 2008, McNemar's test.

$p = 0.003$ for linear trend), and higher WMI scores than non-drinkers ($p = 0.03$ and $p = 0.03$ for linear trend). There were no significant effects of alcohol on the ADI score or the PSI.

*5. Association between cognitive function and physical activity*

The PSI was higher in those women performing strenuous physical activity compared to inactive subjects ($p = 0.02$; $p = 0.02$ for linear trend across categories). However, there were no significant effects of physical activity on the MMSE score, the ADI, VDI, or the WMI.

*6. Changes in lifestyle factor-cognitive function associations across time*

Changes across time for each of the five outcomes were similar between lifestyle categories (Fig. 1) with no evidence of any significant time x lifestyle-factor interaction effects (Table 3). There were no significant differences in the between-subject and within-subject effects for any of the three lifestyle factors across any of the measures of cognitive function except for the effects of smoking on PSI, indicating that use of a single weighted average of within and between-subject effects (Table 3) was appropriate. There were no significant ApoE-$\varepsilon$4 genotype interaction effects with smoking, drinking, or physical activity for each outcome.

*Sensitivity analysis*

The pattern of missingness in the data appeared to be mostly non-informative; those that did not complete cognitive testing for all three phases of the study ($n = 116$) were not different to those that did ($n = 373$) in terms of smoking status ($\chi^2 = 0.20$, 2df, $p = 0.91$), and levels of physical activity ($\chi^2 = 3.04$, 3df, $p = 0.39$) but drank slightly less ($\chi^2 = 11.0$, 3df, $p = 0.012$). Adjusted marginal means were similar for the complete case analysis, indicating the effects amongst those subjects who did not complete the study were not different to those that did, and that data was likely to be missing at random in regards to the lifestyle factors.

## DISCUSSION

Although it has been generally thought that cognitive decline does not usually occur until around age 60, recent data suggests that significant declines in all aspects of cognitive performance begin as early as 45 in both men and women [1]. The harmful association between cardiovascular disease risk factors and risk of cognitive decline [30] suggests that lifestyle interventions that reduce cardiovascular risk may also reduce risk of cognitive decline. In our prospective study of middle aged to older Australian women, despite their high overall cognitive performance, we were able to detect independent and consistent associations across time for smoking, drinking, and physical activity on five different measures of cognitive function.

The observed effects of alcohol were similar to those of a cross-sectional study containing middle to older aged men and women [16]. Light to moderate alcohol consumption is associated with fewer cerebral white matter lesions and brain infarcts compared to either abstinence from alcohol or heavy consumption [31]. Conversely, excessive alcohol intake may

Table 3
Independent effects of alcohol, smoking, physical activity, survey year and age at baseline (2001) on MMSE, ADI, VDI, WMI and PSI[1]

| | MMSE β (95% CI) | ADI β (95% CI) | VDI β (95% CI) | WMI β (95% CI) | PSI β (95% CI) |
|---|---|---|---|---|---|
| Alcohol | | | | | |
| Non-drinker | Referent | Referent | Referent | Referent | Referent |
| Occasional drinker | 0.03 (−0.19, 0.26) | 1.72 (−0.41, 3.86) | 1.88 (−0.67, 4.43) | **3.26 (1.14, 5.37)** | −0.25 (−2.10, 1.59) |
| Light drinker | 0.19 (−0.02, 0.39) | 1.92 (−0.24, 4.08) | **3.52 (1.07, 5.97)** | **2.87 (0.77, 4.97)** | 0.57 (−1.32, 2.46) |
| Mod/Heavy drinker | **0.32 (0.04, 0.61)** | 1.66 (−1.26, 4.58) | **4.33 (0.96, 7.70)** | **3.21 (0.34, 6.07)** | 0.79 (−1.78, 3.35) |
| Linear trend | **0.11 (0.02, 0.19)** | 0.58 (−0.32, 1.48) | **1.54 (0.52, 2.56)** | **0.99 (0.11, 1.87)** | 0.33 (−0.45, 1.13) |
| Global *p*-value | 0.08 | 0.34 | 0.03 | 0.02 | 0.72 |
| Alcohol x year interaction[2] | 0.06 | 0.70 | 0.57 | 0.09 | 0.28 |
| Smoking | | | | | |
| Never smoked | Referent | Referent | Referent | Referent | Referent |
| Previous smoker | −0.05 (−0.22, 0.12) | 0.65 (−1.42, 2.73) | 1.95 (−0.22, 4.11) | **−2.56 (−4.52, −0.61)** | **−1.99 (−3.84, −0.14)** |
| Current smoker | **−0.35 (−0.64, −0.06)** | −1.64 (−5.07, 1.79) | **−3.91 (−7.57, −0.26)** | **−3.42 (−6.67, −0.18)** | **−5.89 (−8.91, −2.87)** |
| Linear trend | −0.12 (−0.25, 0.00) | −0.35 (−1.89, 1.19) | −0.53 (−2.15, 1.09) | **−1.98 (−3.43, −0.54)** | **−2.64 (−4.00, −1.27)** |
| Global *p*-value | 0.06 | 0.38 | 0.004 | 0.02 | <0.001 |
| Smoking x year interaction[2] | 0.61 | 0.77 | 0.80 | 0.33 | 0.86 |
| Physical activity | | | | | |
| Inactive | Referent | Referent | Referent | Referent | Referent |
| Light activity | **0.22 (0.02, 0.41)** | 0.60 (−1.04, 2.23) | 1.13 (−0.95, 3.20) | 1.47 (−0.18, 3.13) | 1.06 (−0.33, 2.45) |
| Moderate activity | 0.21 (−0.06, 0.48) | −0.73 (−3.00, 1.54) | 2.80 (−0.11, 5.72) | 0.60 (−1.72, 2.92) | 1.84 (−0.11, 3.79) |
| Strenuous activity | **0.28 (0.04, 0.52)** | 0.78 (−1.27, 2.83) | 1.37 (−1.24, 3.99) | 1.77 (−0.32, 3.86) | **2.14 (0.37, 3.90)** |
| Linear trend | 0.07 (−0.01, 0.14) | 0.10 (−0.53, 0.73) | 0.42 (−0.39, 1.23) | 0.36 (−0.28, 1.01) | **0.66 (0.11, 1.20)** |
| Global *p*-value | 0.12 | 0.39 | 0.31 | 0.23 | 0.10 |
| Activity x year interaction[2] | 0.36 | 0.81 | 0.22 | 0.56 | 0.89 |
| Survey year | | | | | |
| 2001 | Referent | Referent | Referent | Referent | Referent |
| 2005 | −0.10 (−0.24, 0.04) | **3.43 (2.37, 4.49)** | **3.88 (2.48, 5.28)** | −0.87 (−1.96, 0.22) | **4.71 (3.81, 5.62)** |
| 2008 | **−0.43 (−0.59, −0.28)** | **7.77 (6.61, 8.93)** | **9.88 (8.33, 11.41)** | **3.78 (2.57, 4.99)** | **4.84 (3.83, 5.85)** |
| Linear trend (per y) | **−0.06 (−0.08, −0.04)** | **1.09 (0.92, 1.25)** | **1.36 (1.14, 1.58)** | **0.45 (0.28, 0.63)** | **0.75 (0.61, 0.90)** |
| Global *p*-value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Age at baseline (y) | | | | | |
| 40–49 | Referent | Referent | Referent | Referent | Referent |
| 50–59 | −0.22 (−0.52,0.08) | 0.66 (−3.04, 4.36) | 1.56 (−2.24, 5.35) | −0.78 (−4.22, 2.66) | −1.76 (−5.09, 1.56) |
| 60–69 | **−0.37 (−0.73, −0.01)** | 3.73 (−0.66, 8.13) | 1.13 (−3.36, 5.61) | 0.41 (−3.67, 4.49) | −0.97 (−4.90, 2.97) |
| 70+ | **−1.13 (−1.53, −0.74)** | 3.55 (−1.43, 8.52) | −0.43 (−5.44, 4.59) | 0.79 (−3.78, 5.36) | −2.90 (−7.32, 1.53) |
| Linear trend (10 y) | **−0.44 (−0.58, −0.31)** | 1.39 (−0.30, 3.08) | −0.06 (−1.76, 1.64) | 0.43 (−1.12, 1.98) | −0.77 (−2.28, 0.73) |
| Global *p*-value | <0.001 | 0.27 | 0.64 | 0.82 | 0.47 |

[1]Estimated using a mixed effects linear regression model including alcohol, smoking, physical activity, survey year, and baseline age in 2001, and adjusted for BMI, level of education, menopausal status, ApoE risk, hypertension, dyslipidemia, diabetes, recent psychological distress, marital status, and work status. [2]Each lifestyle factor x year interaction effect was assessed by separately adding lifestyle effect x survey year interaction terms in each outcome model with survey year included as a categorical variable. MMSE, Mini-Mental State Examination; ADI, Auditory Delayed Index; VDI, Visual Delayed Index; WMI, Working Memory Index; PSI, Processing Speed Index.

impair cognitive performance via alcohol induced thiamine deficiencies [32], reduced cerebral glucose metabolism, reduced cerebral blood flow, and frontal lobe dysfunction [33]. Although non-drinkers are typically older, less educated, less physically active, more likely to have lower household incomes, and consume a diet with low vegetable intake and higher fat content [34], our findings of a protective effect remained after adjustment for age, education, levels of physical activity, and employment status. Although it is possible that those who drank less chose to do so because of known poor health status, our results remained significant after adjustment for the presence of hypertension, hyperlipidemia, and clinic blood pressure. The tendency for individuals to under-report their alcohol consumption would only have biased our results if the differences between actual and reported consumption was related to participants' cognitive function.

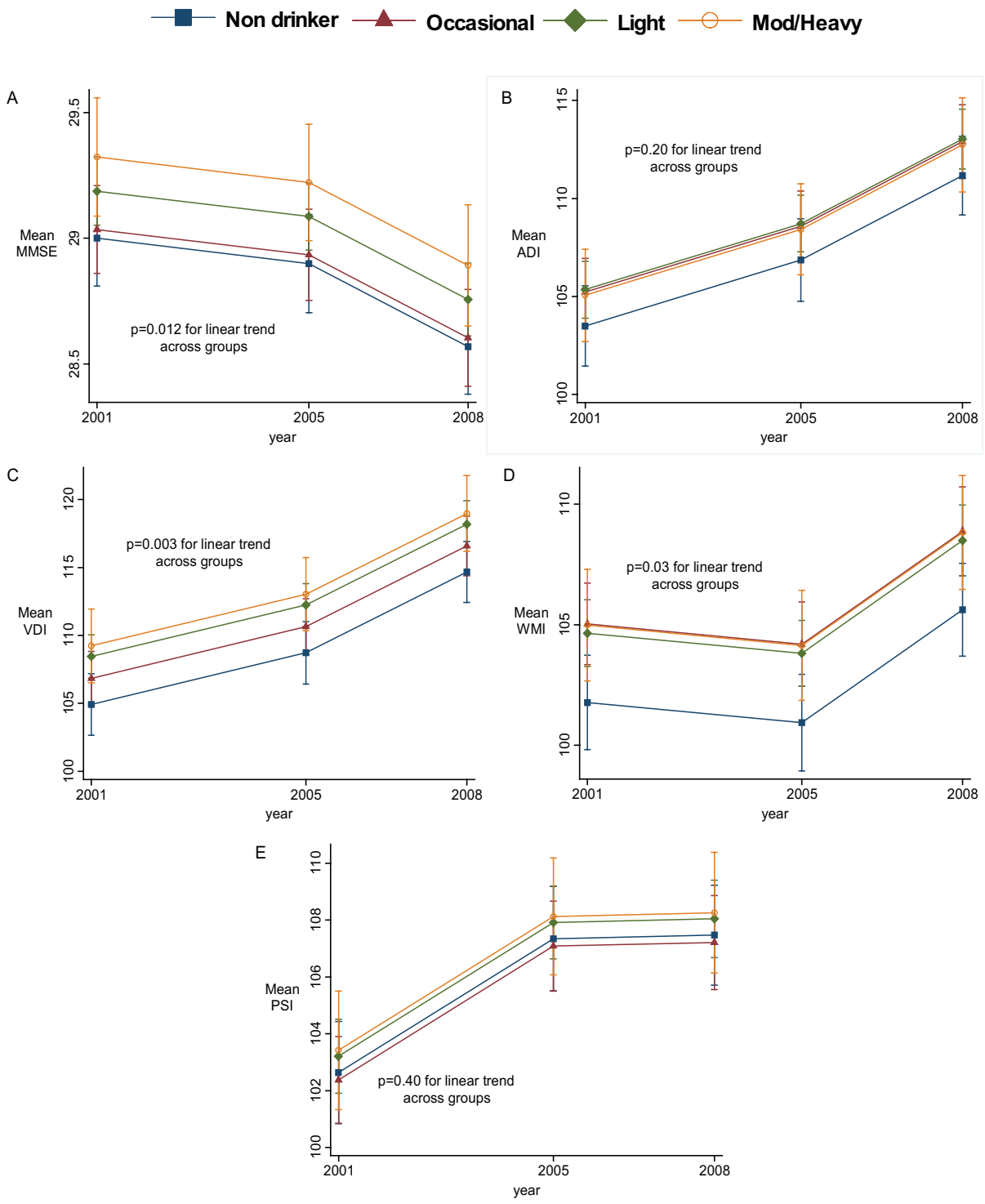


Fig. 2. Adjusted predicted mean (95% CI) cognitive scores from 2001 to 2008 according to drinking status ($n = 489$); obtained from mixed-effects linear regression; adjusted for lifestyle factors (smoking, drinking and physical activity), age, survey year, BMI, level of education, menopausal status, ApoE risk, hypertension, dyslipidemia, diabetes, recent psychological distress, marital status, and employment status.

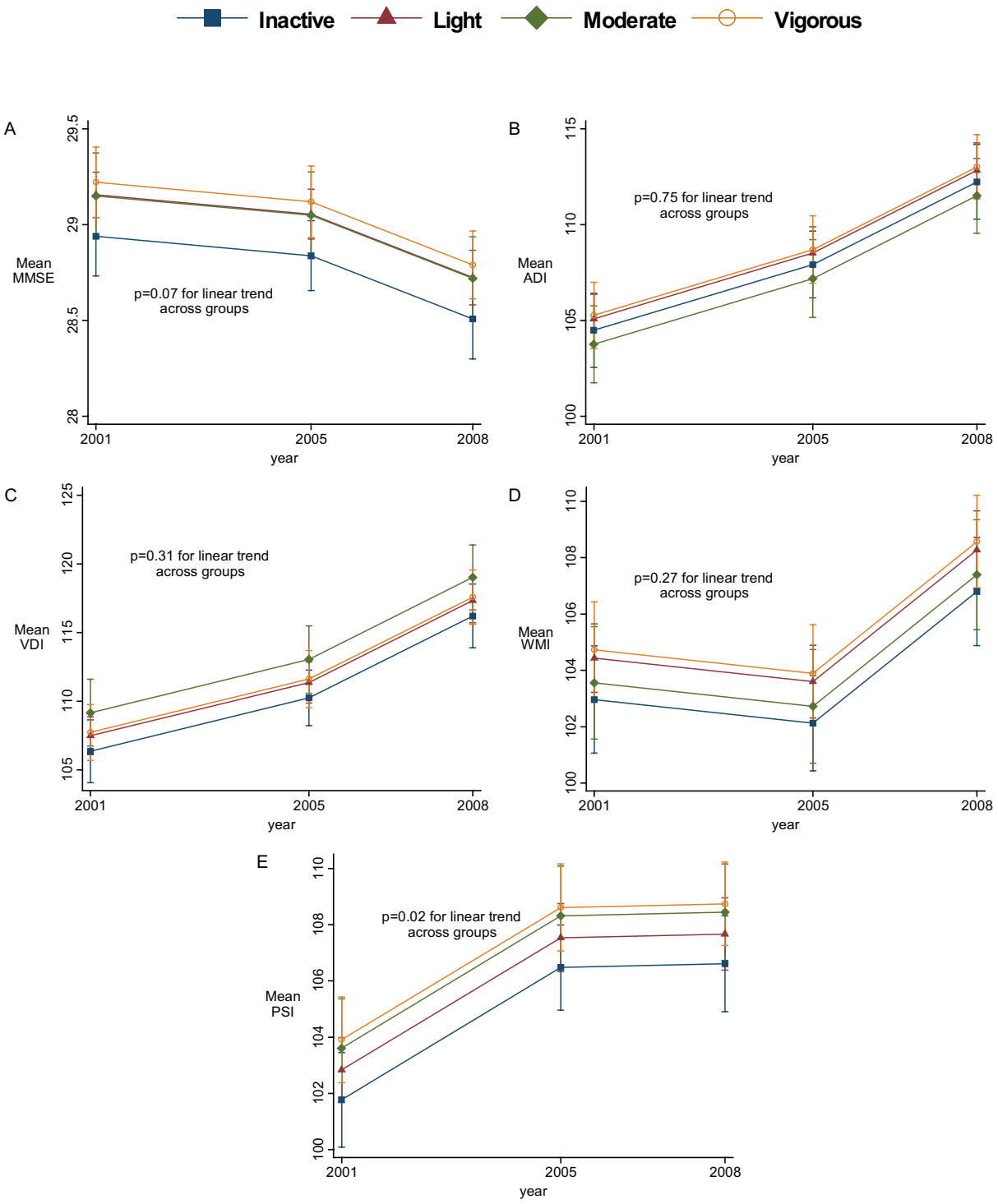


Fig. 3. Adjusted predicted mean (95% CI) cognitive scores from 2001 to 2008 according to physical activity status ($n = 489$); obtained from mixed-effects linear regression; adjusted for lifestyle factors (smoking, drinking and physical activity), age, survey year, BMI, level of education, menopausal status, ApoE risk, hypertension, dyslipidemia, diabetes, recent psychological distress, marital status, and employment status.

Current smokers performed worse than past-smokers and especially worse than never-smokers on the MMSE, VDI, WMI, and PSI. The observed effects on the MMSE were similar in magnitude to a 10-year increase in age. Our results contrast with those of the recently published Whitehall II study [8], in which male but not female smokers showed an increased decline in global and executive function over 10-years. The differences between genders in the Whitehall II study could not be explained although the authors speculated that women smokers may have consumed less than men. The significant between-subject effect of smoking for the PSI rather than any within-subject effects indicates that any reversal of declines in cognitive function from quitting smoking may occur over more extended periods. However, the within-subject effect estimate was based on only 19 subjects who changed their smoking status.

We observed a linear increase for the PSI with increasing intensities of physical activity. Protective effects from greater intensity rather than quantity alone have been reported elsewhere [35, 36] as well as its domain-specific nature including cognitive speed and visual attention [10]. Potential biological mechanisms for these associations include increased insulin-like growth factor I, neurotransmitters, and brain-derived neurotrophic factor [37]. These physical changes may contribute to the vascular and stress hypotheses which are postulated mechanisms for protection against Alzheimer's disease and dementia [38]. Exercise may also influence the proposed cognitive reserve capacity in which functioning continues to be normal despite evidence of physical damage [38]. For a given level of clinical deficit, the greater the level of regular physical activity the greater the level of brain pathology among patients with Alzheimer's disease, indicating stronger cognitive reserve capacity in those that exercise more [39].

We did not observe significant effects of lifestyle across all aspects of cognitive function that were tested. This may either indicate domain specific effects of lifestyle factors, residual confounding, or that effects were too small in certain domains thereby reducing statistical power. However, all non-significant linear trends were in the anticipated direction with positive directional effects of exercise for ADI/VDI/WMI, positive effects for drinking and ADI/PSI, and negative effects for smoking and ADI. We also did not observe differences in the rates of decline between the various sub-groups during follow-up, agreeing with others [30] but in contrast to studies with generally older populations and greater cognitive impairment, where the harmful effects of smoking [8, 40], drinking [15], and physical inactivity [36, 41] accelerated the decline.

The major strengths of our study were the prospective design, the measurement of cognitive performance across different domains, the assessment of all three lifestyle factors, and the adjustment for a large number of potential confounders including socio-demographics, health status, psychological distress, and the APOE-$\varepsilon$4 allele cognitive decline risk modifier. The differences in cognitive functioning between categories of lifestyle behavior were also consistent across all three phases, thereby reducing the potential for bias due to practice effects which were evident for some outcomes [42].

There are a number of limitations to the study. Due to different physical activity surveys being used in 2008, some participants may have been incorrectly classified higher for that year. However, if moderate-to-vigorous activity is protective on cognitive function, then the estimated benefits will be conservative. Second, residual confounding may exist since we could not adjust for some socio-economic factors such as income which predicts cognitive decline [2]. Third, the volunteers that took part had slightly healthier lifestyles than the general Australian/Queensland populations and our results may therefore not be generalizable to all women. However, since this will have reduced variability in the data, the estimated associations are likely to be conservative. Finally, our inability to detect any influence of lifestyle on changes in cognition over time may have been due to the relatively young population thereby diminishing the effects. A larger and slightly older cohort showing more rapid cognitive decline is probably required to better capture any differential effects of lifestyle.

This study provides evidence that smoking has harmful effects on cognitive function in middle-to-older aged women and that there appears to be dose-response protective effects of physical activity and alcohol up to moderate levels of alcohol consumption. Future studies might aim to determine longer term trajectories of cognitive change according to lifestyle behaviors, the extent to which lifestyle modification affect these trajectories, and the mechanisms underlying domain specific effects.

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