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## Cognitive impairment and cardiovascular medication use: Results from wave 1 of The Irish Longitudinal Study on Ageing.

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**Title:** Cognitive impairment and cardiovascular medication use: Results from Wave 1 of The Irish Longitudinal Study on Ageing

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#### Abstract

**Aim:** To explore the association between cardiovascular medication use and cognitive impairment in adults aged 50 years and over.

**Method:** This cross-sectional linked database study involved secondary quantitative analysis of 1,903 participants from wave 1 of the Irish Longitudinal Study on Ageing with available pharmacy claims data. Cognitive impairment was assessed using a cut-off of  $\leq 23$  on the

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Montreal Cognitive Assessment. Cardiovascular medication use was calculated using the proportion of days covered for antihypertensive, antithrombotic, and lipid-modifying medications. For each class of cardiovascular medication, participants were categorised as belonging to one of three medication use groups: 1) not dispensed any medications (reference); 2) poor adherence (proportion of days covered <80%); and 3) good adherence (proportion of days covered  $\geq$ 80%).

**Results:** Controlling for demographic and health variables, there was no evidence of an independent association between impaired cognitive function and use of antihypertensives [good adherence OR (95% CI): 1.16 (0.88, 1.52), poor adherence OR (95% CI): 1.39 (0.95, 2.04)]; antithrombotics [good adherence OR (95% CI): 1.26 (0.93, 1.70), poor adherence OR (95% CI): 1.13 (0.80, 1.59)]; or lipid-modifying agents [good adherence OR (95% CI): 0.95 (0.71, 1.25), poor adherence OR (95% CI): 0.88 (0.64, 1.22)].

**Conclusion:** We found no evidence of an association between cardiovascular medication use and cognitive function. Future studies should investigate the prospective associations between cognition and use of cardiovascular medications using longitudinal data.

**Keywords:** medication adherence, cardiovascular diseases, hypertension, dyslipidemia, cognition disorders, aged.

## Introduction

Cognitive impairment is common among older adults, can range from mild to severe, and is characterised by deterioration in memory, attention, learning, reaction time and executive function.<sup>1,2</sup> Cognitive impairment adversely affects independence, including the ability to adhere to prescribed treatments and medications, which can further impact health.<sup>2,3</sup> Midlife cardiovascular risk factors, including hypertension and dyslipidemia, have been associated with an increased risk of cognitive decline in later life.<sup>3</sup> Associations between cardiovascular risk factors and cognitive impairment have also been reported cross-sectionally, suggesting that appropriate risk factor management may reduce the risk of cognitive impairment.<sup>4-8</sup> However, while observational studies have reported associations between cardiovascular risk factors and cognition, clinical trial evidence on whether risk factor treatment through the use of cardiovascular medications could delay cognitive decline remains inconclusive.<sup>3,5,7</sup>

While some studies have reported potential adverse cognitive effects of some cardiovascular medications, including statins,<sup>9</sup> a meta-analysis of placebo-controlled RCTs reporting cognitive outcomes found no evidence of adverse effects of statins on cognitive function in participants who were either cognitively normal, or who had Alzheimer's Disease.<sup>10</sup> Similarly, an RCT investigating the effects of withdrawal of antihypertensive treatment on cognitive functioning of persons aged 75 and older found that discontinuation of antihypertensive medications did not improve cognitive function. However, a recent review concluded that trial evidence for the beneficial effect of lowering blood pressure or cholesterol on cognitive decline is weak.<sup>11</sup> A number of methodological problems were noted, including variability in cognitive assessments, clinical endpoints and inclusion criteria, high numbers of actively treated persons in control arms, high discontinuation rates, and shorter follow-up periods.<sup>3,5,11</sup> Finally, poor medication adherence may attenuate treatment effects, with some clinical trials reporting adherence rates of 43% to 78%.<sup>12,13</sup>

#### *Cognitive impairment and cardiovascular medication use*

Medication adherence is essential for managing chronic conditions, as non-adherence is associated with increased morbidity, mortality, and higher costs of care.<sup>14-17</sup> However, adherence to cardiovascular medications is often poor, with a meta-analysis of 20 studies reporting an adherence estimate of 57% (95% CI 50, 64).<sup>18</sup> Medication adherence requires various cognitive skills, including scheduling medications, understanding directions, and problem solving in relation to missed doses, all of which can be adversely affected by cognitive impairment.<sup>14,19</sup> Poor adherence could in turn lead to further cognitive decline, as well as increasing the risk of cardiovascular events and stroke.<sup>6,12</sup> Given the prevalence of sub-optimal adherence, it is important to consider the extent to which patients actually adhere to medications when assessing the impact of drug treatment on outcomes.

#### *Aim*

The aim of this study was to explore the association between cardiovascular medication use and cognitive impairment in a population-based cross-sectional study of community-dwelling adults aged 50 years and over.

## Methods

### *Design and data sources*

This cross-sectional linked database study involved secondary quantitative analysis of a sub-sample of participants from wave 1 of the Irish Longitudinal Study on Ageing (TILDA),<sup>20,21</sup> with available data on dispensed prescription medications from the Irish Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database. This database provides details on monthly-dispensed medications for each individual in the scheme. Access to the scheme, which provides free general practitioner and hospital visits, and prescription medications at minimal cost, is means-tested for persons aged <70 years, with a substantially higher income threshold for over 70s.<sup>22</sup> Over 90% of adults over the age of 70 in Ireland are eligible for the scheme. Members of the scheme are thus representative of the over-70s in Ireland; however, among those under the age of 70, women and those in lower socio-economic groups are over-represented.<sup>23</sup>

### *Participants*

The target population for wave 1 of The Irish Longitudinal Study on Ageing was the population of the Republic of Ireland aged 50 or over living in residential addresses (not in a long-term care institution), and their spouses or partners.<sup>21,24</sup> Participants with known or suspected dementia were not recruited.<sup>24,25</sup> In total, 8,175 adults aged 50 years and over (62% household response rate) participated in wave 1 of TILDA. Computer-assisted personal interviews took place between October 2009 and February 2011. Sampling, recruitment, and data collection have been described elsewhere.<sup>20,21</sup> HSE-PCRS records were successfully linked for 3,120 TILDA wave 1 participants (38.2%).<sup>22</sup> Of these, 2,149 completed cognitive assessments. We excluded participants if interviewers indicated the presence of at least one of a list of factors that could have affected performance during cognitive assessments (e.g. interruptions, noisy environment, hard of hearing, too tired; n=107). Of the remaining participants, 1,903 had blood pressure measurements and blood lipid profiles, forming the sample for this analysis (Figure 1). As this is a community sample, participants included those prescribed cardiovascular medications for both primary and secondary prevention purposes (for more detailed demographic data on the full TILDA sample, as well as the sub-sample with available linked prescription claims data, please see appendix 1).

As the present analysis was limited by the data available for participants in wave 1 of TILDA with cognitive and health assessments and linked prescription claims, a formal power calculation was not conducted. However, given the sample size of 1,903, our study would have had sufficient power to detect an odds ratio of 1.36 or greater for the association between medication use and cognitive impairment, assuming a baseline rate of cognitive impairment of 37%, 80% power and 5% level of significance.

### *Cognition*

Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), a 30-point<sup>1</sup> tool that assesses attention, orientation, language, verbal memory, visuospatial and executive function, and can be completed in approximately 10 minutes.<sup>26</sup> The MoCA was developed to detect mild cognitive impairment and is more sensitive than the Mini Mental State Examination when applied to cognitively intact older adults.<sup>26</sup> Several authors have recommended caution when applying the original cut-off of 26 to identify individuals with cognitive impairment, as it has repeatedly yielded low levels of specificity.<sup>27-29</sup> Indeed, a score of <26 identified more than half of our sample as cognitively impaired. This is higher than would be expected given the prevalence of cognitive impairment, particularly as participants with severe impairments and dementia were excluded from wave 1 of TILDA.<sup>21,28</sup> A number of authors have recommended a cut-off of ≤23 to identify individuals with definite impairments in cognitive function.<sup>27,30,31</sup> We thus applied this more conservative cut-off in the present study.

### *Cardiovascular medication use*

In order to assess the association between cardiovascular medication use and cognitive impairment, we considered medications commonly used to control cardiovascular risk factors. Medications were coded according to the World Health Organization Anatomic Therapeutic Chemical (ATC) Classification,<sup>32</sup> and categorised according to main therapeutic group: antihypertensives (ATC codes C02, C03, C07, C08, C09), antithrombotics (anticoagulant and antiplatelet agents, B01A), and lipid-modifiers (C10).

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<sup>1</sup> Participants with less than 12 years of formal education receive one additional point

Medication use in the 365 days prior to TILDA interview was determined using pharmacy claims data, which is commonly used and provides an objective method of estimating medication use for large populations.<sup>13,17,18</sup> We calculated the total proportion of days covered (PDC) as the sum of the days supplied for medications within each medication class divided by the number of days in the study period.<sup>33,34</sup> At least two prescription fill dates are required for each drug to calculate this ratio. PDC was capped at 1 (100%, 365 days covered).<sup>15</sup> We used a cut-off of  $\geq 80\%$  to identify good adherence. This cut-off is generally considered sufficient for populations with, or at risk of, cardiovascular disease, presents a reasonable balance between sensitivity and specificity, and has been associated with cardiovascular outcomes.<sup>15,17,33,34</sup> In order to assess the association between use of antihypertensive, antithrombotic and lipid-modifying medications, and cognitive impairment, respondents were categorised into one of three groups for each of the three medication classes: 1) no medication use (not dispensed any medications; reference group); 2) poor adherence (PDC $<80\%$ ); and 3) good adherence (PDC  $\geq 80\%$ ).

#### *Health assessment*

All participants completed a home or health-centre based health assessment, including blood pressure (BP) measurement and complete venous blood lipid profiles. Hypertension was categorised as a mean systolic or diastolic reading of  $>140\text{mmHG}$  or  $>90\text{mmHG}$ , respectively<sup>35</sup>. Respondents with total cholesterol  $>5\text{mmol/L}$  ( $193\text{mg/dl}$ ) were considered to have high cholesterol. TILDA participants were not requested to fast for the health assessment, due to difficulties coordinating fasting and travel for a large national sample.<sup>36</sup>

#### *Covariates*

Covariates included age (50-64, 65-74 or 75+ years), sex, education (none/primary school, secondary school or third/higher level) marital status (married or single/widowed/divorced), living situation (alone or with others), employment status (working or not working), location (urban or rural), lifelong learning (any education or training in the previous 12 months), social participation (any monthly social activity), disability (any ADL or IADL impairment), hypertension (systolic/diastolic BP  $>140/90\text{mmHG}$ ), high cholesterol (total cholesterol  $>5\text{mmol/L}$  ( $193\text{mg/dl}$ )), BMI (overweight/obese or normal), depressive symptoms (none or moderate/severe), smoking (current or past/never), and regular physical activity (none or moderate/high). Additionally, participants were categorised into

one of two groups (definite anticholinergic burden or no anticholinergic burden) based on whether or not they had been dispensed any medications listed as possessing definite anticholinergic properties on the anticholinergic cognitive burden scale during the study period, as anticholinergic burden is associated with cognitive impairment.<sup>37</sup>

#### *Data analysis*

Descriptive statistics, including frequencies and percentages, were used to summarise the data. Unadjusted associations between clinical, demographic and lifestyle variables and cognitive impairment were assessed with chi-square tests. Unadjusted and adjusted associations between cardiovascular medication use and cognitive impairment were estimated using logistic regression models, with goodness of fit assessed using the Hosmer and Lemeshow test. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) are presented. Multivariate models were adjusted for age, sex, hypertension, high cholesterol, smoking, as well as covariates associated with cognitive impairment at the  $p < 0.10$  level in univariate analyses (living situation was excluded from multivariate models due to collinearity with marital status). Data were analysed using Stata 14 (StataCorp LP, 2015). The  $\alpha$ -level was set at 0.05, with a sequential Holm-Bonferroni correction for all bivariate associations to adjust for multiple comparisons.

## **Results**

### *Cognitive impairment*

A total of 715 respondents (37.6%) were classified as cognitively impaired according to a MoCA score  $\leq 23$ . Unadjusted associations between demographics, health variables, medication use, and cognitive impairment are shown in Table 1. Respondents who were older, not married, living alone, or living in a rural location were more likely to be classified as cognitively impaired, compared to respondents who were younger, married, living with others, or living in an urban location. Participants who were engaged in lifelong learning, a monthly social activity, or regular physical activity were less likely to be classified as cognitively impaired compared to those not engaged in these activities. Cognitive impairment was also more common among respondents with moderate or severe depressive symptoms, an ADL or IADL disability, and lower levels of education.

In unadjusted analyses, use of antihypertensive medications was significantly associated with cognitive impairment, regardless of whether adherence was good or poor. Good adherence to antithrombotics was associated with cognitive impairment, compared to those who were not using antithrombotic medications. The use of lipid-modifying medications was not associated with cognitive impairment in univariate analyses (Table 1).

#### *Cardiovascular medication use and cognitive impairment*

Table 2 illustrates a logistic regression model of cognitive impairment based on use of antihypertensive, antithrombotic, and lipid-modifying medications. This model was statistically significant and a good fit of the data [ $\chi^2(21)=202.52, p<0.001$ ; Hosmer and Lemeshow,  $p=0.479$ ]. When controlling for demographic and health variables, there was no evidence of an independent association between cognitive function and either poor adherence [adjusted OR (95% CI): 1.39 (0.95, 2.04)], or good adherence [adjusted OR (95% CI): 1.16 (0.88, 1.52)] to antihypertensive medications. Similarly, use of antithrombotic medications was not associated with impaired cognitive function, regardless of whether adherence was poor [adjusted OR (95% CI): 1.13 (0.80, 1.59)], or good [adjusted OR (95% CI): 1.26 (0.93, 1.70)]. There was no evidence of a difference in cognitive function between respondents who were not using lipid-modifying medications and those with poor adherence [adjusted OR (95% CI): 0.88 (0.64, 1.22)] or good adherence [adjusted OR (95% CI): 0.95 (0.71, 1.25)].

#### **Discussion**

This population-based study of adults aged 50 years and over found no evidence of an independent association between cognitive impairment and use of antihypertensive, antithrombotic, or lipid-modifying medications, irrespective of whether medication adherence was good or poor. Previous research has reported mixed findings regarding associations between the use of cardiovascular medications and cognitive impairment, with weak evidence that treatment of cardiovascular risk factors prevents cognitive decline<sup>3,11</sup>. Suboptimal medication adherence attenuates treatment effects and may be partly responsible for the variation in drug treatment responses<sup>4,12</sup>. However, few studies have explicitly included adherence to cardiovascular medications when assessing the association of medication use and cognitive function.

As this study is based on cross-sectional analyses, it was not possible to assess prospective associations between longer-term cardiovascular medication use and cognitive impairment, or to consider decline in cognitive function. The effects of medication (non)use on cognitive impairment may not manifest for several years. This could help to explain the weak evidence of a beneficial effect of treatment of cardiovascular risk factors on cognitive decline from randomised controlled trials, as follow-up times may be too short to detect an effect on cognition <sup>11</sup>. Longitudinal studies are therefore needed to investigate whether effective cardiovascular risk factor management could modify cognitive decline <sup>4</sup>. Future studies could examine these associations prospectively, as data collection for subsequent waves of TILDA is currently ongoing.

#### *Strengths and limitations*

This study has a number of strengths, including a large sample and objective measures of hypertension and hypercholesterolaemia. Our study also highlights the importance of adjusting for potential confounders when examining the association between medication use and cognitive impairment, particularly as increasing age is associated with both a growing number of prescribed medications, and an increased risk of cognitive impairment. We were able to control for a large number of potentially confounding factors and found significant attenuation of the association between cardiovascular medication use and cognitive function in our multivariate model. Inadequate control for confounding may help to explain the disparity in findings between experimental and observational studies.

Unlike other studies utilising data from closed pharmacy systems, such as veteran health organisations <sup>1</sup>, this study included a large, national, population-based sample. It is, to our knowledge, the first to examine the association between cardiovascular medication use and cognitive impairment through pharmacy claims data linked to a national population cohort. The use of prescription data is efficient and provides an objective and non-invasive estimate of adherence that is comparable to electronic measures, and a more accurate reflection of real-world medication use compared with clinical trials <sup>34</sup>.

A number of limitations should be noted. The use of prescription refill data has been described as providing a “sparse” view of adherence, and may have introduced bias by overestimating medication use, as some participants with filled prescriptions may not have taken their medications.<sup>16,18</sup> Further, it is not known for how long participants included in the present study had been taking cardiovascular medications prior to inclusion in this study. Conversely, individuals not dispensed medications are likely to be a heterogeneous group, and could include a substantial number of respondents who were prescribed medications but did not fill their prescriptions<sup>34</sup>. Further, while a cut-off of 80% is frequently used to indicate adequate medication adherence, and appears reasonable for cardiovascular medications, the actual deviations from prescribed medication regimens necessary to adversely affect treatment effects may vary between different medications<sup>15,16</sup>.

Dispensing data were available for a sub-sample of all TILDA participants. These participants were older, had less education, lower incomes, and fewer were employed than in the overall TILDA sample<sup>22</sup>. They also reported more chronic diseases, medications, and depressive symptoms. Additionally, participants who did not have cognitive or objective health assessments were more likely to be older and have lower levels of education than those with cognitive and health assessments, which may affect the generalizability of these findings. The fact that cognitive assessments and objective health measures were available for a sub-sample of respondents may be an indication of the perceived invasiveness or sensitivity of these types of assessments<sup>38</sup>. This is not unique to this study. Mindell et al. note that participation rates for survey health examinations in Europe have fallen, with fewer respondents having blood sample, weight, and blood pressure measurements than are interviewed overall<sup>38</sup>. In our study, participants without these assessments were more likely to be older and to have lower levels of education, which may have introduced bias, as both age and education are associated with cognitive function. Finally, people with known or suspected dementia were not recruited for wave 1 of TILDA<sup>24,25</sup>. Therefore, individuals with more severe forms of cognitive impairment were not included in this study, and the true association between cognitive impairment and (non)use of cardiovascular medications may be underestimated.

In conclusion, given the prevalence of poor adherence to medications for chronic conditions, the extent to which patients actually adhere to medications should be considered when assessing the impact of cardiovascular medication use on outcomes. This is the first study to examine the association between cardiovascular medication use and cognitive impairment using pharmacy claims

data linked to a national population cohort. We found no evidence of an independent association between use of antihypertensive, antithrombotic or lipid-modifying medications and cognitive impairment in this population-based sample of adults aged 50 years and over, irrespective of the level of adherence to these medications.

## **Disclosures**

### *Ethics*

The Faculty of Health Sciences, Trinity College Dublin Research Ethics Committee approved TILDA on 2 May 2008, and all participants gave written informed consent. Wave 1 of TILDA excluded participants who could not personally consent to participation in the study.

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### *Disclosures*

All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work and no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years. DW is an Advisory Board Member for Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb and Bayer, and has received personal fees for this outside the submitted work. DW is Speaker Honorarium for Boehringer Ingelheim, and has received personal fees for this outside the submitted work.

### Author contributions

DR conducted the statistical analysis and drafted and edited the manuscript. KB acquired the data, conceived and designed the study and critically revised the manuscript. AH conceived and designed the study and critically revised the manuscript. DW designed the study and critically revised the manuscript. All authors approved the final draft.

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Researchers interested in using TILDA data may access the data for free from the following sites: Irish Social Science Data Archive (ISSDA) at University College Dublin <http://www.ucd.ie/issda/data/tilda/>; Interuniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan <http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34315>

### References

1. Hawkins LA, Kilian S, Firek A, Kashner TM, Firek CJ, Silvet H. Cognitive impairment and medication adherence in outpatients with heart failure. *Heart Lung*. 2012;41(6):572-582.
2. Institute of Medicine. *Cognitive aging: Progress in understanding and opportunities for action*. Washington DC: The National Academies Press;2015.
3. Ligthart SA, Moll van Charante EP, Van Gool WA, Richard E. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. *Vasc Health Risk Manag*. 2010;6:775-785.
4. Jefferson AL, Hohman TJ, Liu D, et al. Adverse vascular risk is related to cognitive decline in older adults. *Journal of Alzheimer's disease : JAD*. 2015;44(4):1361-1373.
5. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens*. 2013;31(6):1073-1082.

6. Vinyoles E, De la Figuera M, Gonzalez-Segura D. Cognitive function and blood pressure control in hypertensive patients over 60 years of age: COGNIPRES study. *Current medical research and opinion*. 2008;24(12):3331-3339.
7. Walker KA, Power MC, Gottesman RF. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. *Current hypertension reports*. 2017;19(3):24.
8. Muela HC, Costa-Hong VA, Yassuda MS, et al. Hypertension Severity Is Associated With Impaired Cognitive Performance. *J Am Heart Assoc*. 2017;6(1).
9. Mandas A, Congiu MG, Abete C, et al. Cognitive decline and depressive symptoms in late-life are associated with statin use: evidence from a population-based study of Sardinian old people living in their own home. *Neurological research*. 2014;36(3):247-254.
10. Ott BR, Daiello LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med*. 2015;30(3):348-358.
11. Zanchetti A, Liu L, Mancia G, et al. Blood pressure and low-density lipoprotein-cholesterol lowering for prevention of strokes and cognitive decline: a review of available trial evidence. *J Hypertens*. 2014;32(9):1741-1750.
12. Douiri A, McKeivitt C, Emmett ES, Rudd AG, Wolfe CD. Long-term effects of secondary prevention on cognitive function in stroke patients. *Circulation*. 2013;128(12):1341-1348.
13. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.
14. Campbell NL, Boustani MA, Skopelja EN, Gao S, Unverzagt FW, Murray MD. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother*. 2012;10(3):165-177.
15. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028-3035.
16. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*. 2012;73(5):691-705.
17. Packard KA, Hilleman DE. Adherence to Therapies for Secondary Prevention of Cardiovascular Disease: A Focus on Aspirin. *Cardiovascular therapeutics*. 2016.
18. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med*. 2012;125(9):882-887 e881.
19. Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM. The impact of cognitive function on medication management: three studies. *Health Psychol*. 2010;29(1):50-55.
20. Barrett A, Savva G, Timonen V, Kenny RA. Fifty Plus in Ireland 2011. First results from the Irish Longitudinal Study on Ageing (TILDA). Dublin The Irish Longitudinal Study on Ageing; 2011: [https://tilda.tcd.ie/assets/pdf/glossy/Tilda\\_Master\\_First\\_Findings\\_Report.pdf](https://tilda.tcd.ie/assets/pdf/glossy/Tilda_Master_First_Findings_Report.pdf). Accessed 24 July 2017.

21. Kenny RA, Whelan BJ, Cronin H, et al. The design of the Irish longitudinal study on ageing. Dublin: TILDA; 2010: <https://tilda.tcd.ie/assets/pdf/DesignReport2010.pdf>. Accessed 24 July 2017.
22. Richardson K, Kenny RA, Peklar J, Bennett K. Agreement between patient interview data on prescription medication use and pharmacy records in those aged older than 50 years varied by therapeutic group and reporting of indicated health conditions. *J Clin Epidemiol*. 2013;66(11):1308-1316.
23. Rohde D, Williams D, Gaynor E, et al. Secondary prevention and cognitive function after stroke: a study protocol for a 5-year follow-up of the ASPIRE-S cohort. *BMJ Open*. 2017;7(3):e014819.
24. Kenny RA, Coen RF, Frewen J, Donoghue OA, Cronin H, Savva GM. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. *J Am Geriatr Soc*. 2013;61 Suppl 2:S279-290.
25. O'Regan C, Cronin H, Kenny RA. Mental Health And Cognitive Function. In: Barrett A, Savva G, Timonen V, Kenny RA, eds. *Fifty Plus in Ireland 2011: First results from the Irish Longitudinal Study on Ageing (TILDA)*. Dublin: TILDA; 2011.
26. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699.
27. Coen RF, Cahill R, Lawlor BA. Things to watch out for when using the Montreal cognitive assessment (MoCA). *Int J Geriatr Psychiatry*. 2011;26(1):107-108.
28. Kopecek M, Stepankova H, Lukavsky J, Ripova D, Nikolai T, Bezdicek O. Montreal Cognitive Assessment (MoCA): Normative Data for Old and Very Old Czech Adults. *Applied neuropsychology Adult*. 2016:1-7.
29. Waldron-Perrine B, Axelrod BN. Determining an appropriate cutting score for indication of impairment on the Montreal Cognitive Assessment. *Int J Geriatr Psychiatry*. 2012;27(11):1189-1194.
30. Lee JY, Dong Woo Lee Fau - Cho S-J, Cho Sj Fau - Na DL, et al. Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. 2008(0891-9887 (Print)).
31. Luis CA, Keegan Ap Fau - Mullan M, Mullan M. Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. 2009(1099-1166 (Electronic)).
32. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment 2013*. Oslo: World Health Organization;2012.
33. Kronish IM, Ye S. Adherence to cardiovascular medications: lessons learned and future directions. *Prog Cardiovasc Dis*. 2013;55(6):590-600.

34. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *International journal of clinical pharmacy*. 2014;36(1):55-69.
35. The Irish Longitudinal Study on Ageing. Anonymised data release guide, version 2.0.0. 2015. <http://tilda.tcd.ie/publications/study-documents/Documents/Wave 1/TILDA Release Guide v2.0.0.docx>. Accessed 15 December 2015.
36. Cronin H, O'Regan C, Finucane C, Kearney P, Kenny RA. Health and Aging: Development of The Irish Longitudinal Study on Ageing Health Assessment. *Journal of the American Geriatrics Society*. 2013;61:S269-S278.
37. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4(3):311-320.
38. Mindell JS, Giampaoli S, Goesswald A, et al. Sample selection, recruitment and participation rates in health examination surveys in Europe - experience from seven national surveys. *BMC medical research methodology*. 2015;15:78.

**Table 1. Associations between demographic and medication use variables, and cognitive impairment**

Demographic and health variables		No impairment n (%)	Cognitive impairment n (%)	<i>p</i>
<b>Sex</b>	Male	525 (62.3)	318 (37.7)	0.904
	Female	663 (62.6)	397 (37.4)	
<b>Age</b>	50-64 years	467 (69.1)	209 (30.9)	<0.001*
	65-74 years	459 (66.0)	237 (34.0)	
	75+ years	262 (49.3)	269 (50.7)	
<b>Education</b> (n=1,901)	None/primary school	400 (51.0)	385 (49.0)	<0.001*
	Secondary school	497 (66.6)	249 (33.4)	
	Third/higher level	291 (78.7)	79 (21.3)	
<b>Marital status</b>	Married	778 (67.1)	382 (32.9)	<0.001*
	Not married	410 (55.2)	333 (44.8)	
<b>Living situation</b>	Living alone	300 (56.0)	236 (44.0)	<0.001*

	Living with others	888 (65.0)	479 (35.0)	
<b>Location</b> (n=1,901)	Urban (town/city)	655 (66.7)	327 (33.3)	<0.001*
	Rural	531 (57.8)	388 (42.2)	
<b>Lifelong learning</b>	Education/training	135 (82.8)	28 (17.2)	<0.001*
	No education/training	1,053 (60.5)	687 (39.5)	
<b>Employment status</b> (n=1,873)	Working	166 (66.1)	85 (33.9)	0.173
	Not working	1,000 (61.7)	622 (38.3)	
<b>Disability</b>	IADL/ADL disability	168 (50.5)	165 (49.65)	<0.001*
	No disability	1,020 (65.0)	550 (35.0)	
<b>BMI</b>	Healthy weight	259 (65.1)	139 (34.9)	0.220
	Overweight/obese	929 (61.7)	576 (38.3)	
<b>Blood pressure</b>	Hypertension	556 (62.1)	339 (37.9)	0.796
	No hypertension	632 (62.7)	376 (37.3)	
<b>Cholesterol</b>	High cholesterol	526 (65.4)	278 (34.6)	0.021
	No high cholesterol	662 (60.2)	437 (39.8)	
<b>Smoking</b>	Smoker	211 (58.8)	148 (41.2)	0.113
	Non-smoker	977 (63.3)	567 (36.7)	
<b>Physical activity</b> (n=1,891)	None	385 (56.7)	294 (43.3)	<0.001*
	Moderate/High	796 (65.7)	416 (34.3)	
<b>Depressive symptoms</b> (n=1,873)	None/mild	826 (64.5)	455 (35.5)	0.004*
	Moderate/Severe	341 (57.6)	251 (42.4)	
<b>Social Participation</b> (n=1,742)	Monthly social activity	951 (66.2)	485 (33.8)	<0.001*
	No social activity	156 (49.4)	160 (50.6)	
<b>Anticholinergic burden</b>	Definite	36 (49.3)	37 (50.7)	0.0018*
	None	1,152 (63.0)	678 (37.0)	
<b>Antihypertensive</b>	None	644 (67.3)	313 (32.7)	<0.001*

<b>medications</b>	Poor adherence	101 (55.8)	80 (44.2)	
	Good adherence	443 (57.9)	322 (42.1)	
<b>Antithrombotic medications</b>	None	788 (65.7)	411 (34.3)	<0.001*
	Poor adherence	153 (60.0)	102 (40.0)	
	Good adherence	247 (55.0)	202 (45.0)	
<b>Lipid-modifying medications</b>	None	680 (63.8)	386 (36.2)	0.198
	Poor adherence	199 (63.2)	116 (36.8)	
	Good adherence	309 (59.2)	213 (40.8)	

Note: n=1,903 unless otherwise indicated.

\*significant using a Holm-Bonferroni sequentially corrected alpha level

**Table 2. Unadjusted and adjusted OR (95% CI) from logistic regression model of cognitive impairment based on exposure to antihypertensives, antithrombotics, and lipid-modifying medications**

<b>Medication use</b>		<b>Unadjusted Odds Ratio (95% CI)</b>	<b>p</b>	<b>Adjusted Odds Ratio (95% CI)*</b>	<b>p</b>
<b>Antihypertensive medications</b>	<b>None</b>	<b>Ref.</b>		<b>Ref.</b>	
	Poor adherence	1.63 (1.18, 2.25)	0.003	1.39 (0.95, 2.04)	0.094
	Good adherence	1.50 (1.23, 1.82)	<0.001	1.16 (0.88, 1.52)	0.285
<b>Antithrombotic medications</b>	<b>None</b>	<b>Ref.</b>		<b>Ref.</b>	
	Poor adherence	1.29 (0.97, 1.69)	0.083	1.13 (0.80, 1.59)	0.488
	Good adherence	1.57 (1.26, 1.96)	<0.001	1.26 (0.93, 1.70)	0.138
<b>Lipid-modifying medications</b>	<b>None</b>	<b>Ref.</b>		<b>Ref.</b>	
	Poor adherence	1.03 (0.79, 1.33)	0.842	0.88 (0.64, 1.22)	0.457
	Good adherence	1.21 (0.98, 1.51)	0.076	0.95 (0.71, 1.25)	0.694

Note: n=1,710. Nagelkerke R<sup>2</sup>=0.153, Cox-Snell R<sup>2</sup>=0.112.

\*Adjusted for age, sex, education, marital status, location, high cholesterol, hypertension, disability, depressive symptoms, smoking status, physical activity, social participation and anticholinergic burden.

## Figure legends

Figure 1. Flowchart of participants

Appendix 1. TILDA + PCRS (participants with available prescription claims data) demographic and health variables (Wave 1)

		TILDA sample (N=8,504) <sup>†</sup> n, %		TILDA + PCRS (N=3,176) <sup>†</sup> n, %	
<b>Age M (SD)</b>		63.14 (10.21)		68.46 (10.33)	
<b>Age group</b>	<50*	329	3.87	54	1.70
	50-64	4,668	54.89	1,069	33.66
	65-74	2,163	25.44	1,089	34.29
	>=75	1,344	15.80	964	30.35
<b>Male</b>		3,780	44.45	1,381	43.48
<b>Marital status</b>	Married	5,966	70.16	1,871	58.91
	Not married	2,538	29.84	1,305	41.08
<b>Living arrangements</b>	Alone	1,822	21.43	946	29.79
	With others	6,682	78.57	2,230	70.21
<b>Education</b> (n=8,500, 3,174)	Primary/none	2,521	29.66	1,469	46.28
	Secondary	3,431	40.36	1,162	36.61
	Third/higher	2,548	29.98	543	17.11
<b>Employment status</b>	Working	3,141	36.94	413	13.00
	Not working	5,363	63.03	2,763	87.00
<b>Disability</b>	Not disabled	7,500	88.19	2,583	81.33
	IADL/ADL disability	1,004	11.81	593	18.67
<b>Cardiovascular conditions</b>	Hypertension	3,088	36.31	1,483	46.69
	High cholesterol	3,180	37.39	1,273	40.08
	Diabetes	641	7.54	345	10.86

	Angina	452	5.32	284	8.94
	MI	379	4.46	233	7.34
	Stroke	134	1.58	92	2.90
	TIA	177	2.08	103	3.24
	Irregular heart rhythm	599	7.04	308	9.70
	Other CVD	298	3.50	157	4.94
<b>Smoking</b>	Non-smoker	6,939	81.61	2517	79.25
	Smoker	1,564	18.39	659	20.75
<b>Depressive symptoms</b> (n=8,371, 3,122)	None/mild	6,094	72.80	2,102	67.33
	Moderate/severe	2,217	27.20	1,020	32.68
<b>Social participation</b>	No	4,463	52.48	1,832	57.68
	Yes	4,041	47.52	1,344	42.32
<b>Physical activity</b> (n=8,423, 3,151)	None	2,682	31.84	1,214	38.53
	Moderate/high	5,741	68.16	1,937	61.47
<b>Cognition (MoCA)</b> (n=6,112, 2,191)	None ( $\geq 26$ )	3,231	52.86	887	40.48
	Mild (18-25)	2,632	43.06	1,139	51.99
	Moderate or Severe ( $\leq 17$ )	249	4.07	165	7.53

† Unless otherwise indicated

\* Participants under the age of 50 are spouses or partners of recruited participants, and as such, were not randomly selected and are not representative of the population of Ireland aged under 50. Therefore, these participants were excluded from the present study.

