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# Cover page

**Title:**   
Repurposing lipid regulating drugs for the prevention of Alzheimer’s disease

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# Abstract

**Introduction**:

**Methods**:

**Findings**:

**Interpretation**:

**Funding**:

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# Research in context

**Evidence before this study**:

**Added value of this study**:

**Implications of all the available evidence**:

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# Introduction

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# Methods

## CPRD Analysis

## Mendelian randomization analysis

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# Results

## CPRD Analysis

Table of characteristics

Table 1: Patient characteristics of Cohort 2

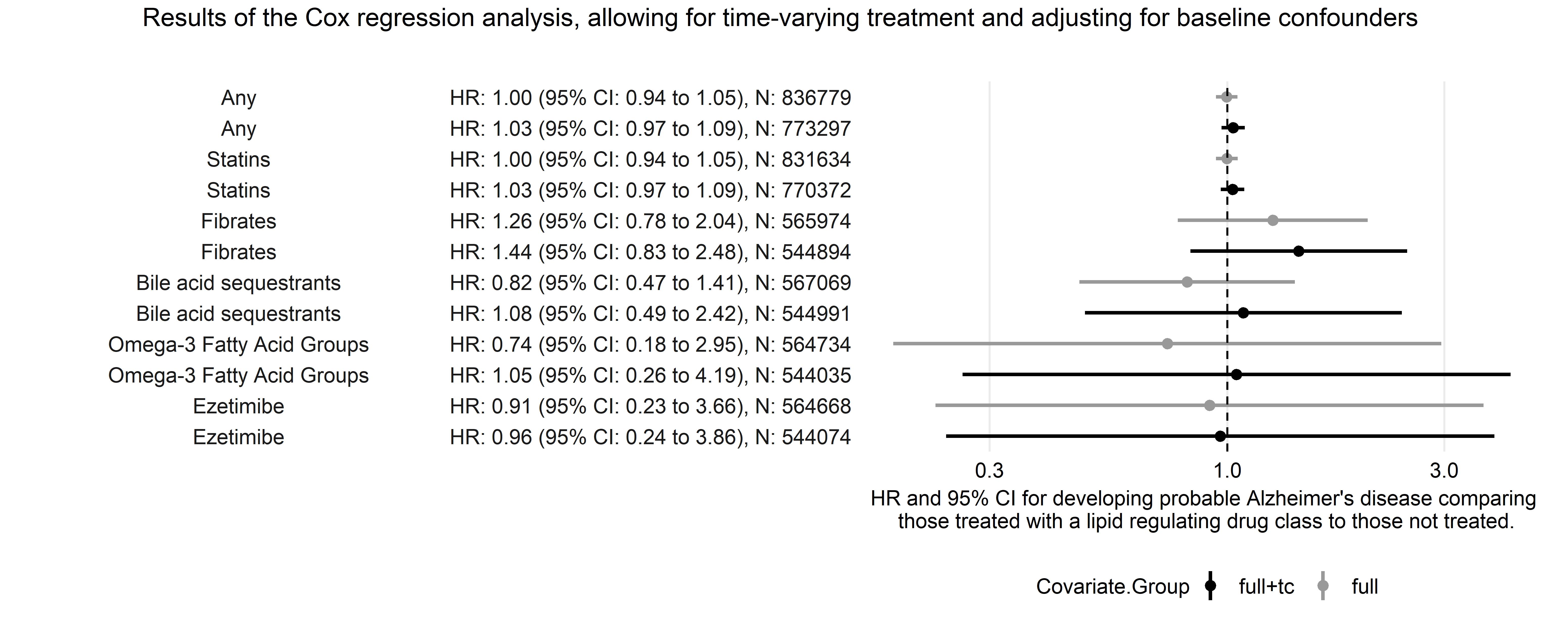
|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Whole Sample | No LRA | Statins | Bile acid sequestrants | Ezetimibe | Ezetimibe & Statins | Fibrates | Nicotinic acid groups | Omega-3 Fatty Acid Groups |
| N | 773387 | 543876 | 226586 | 1199 | 282 | 56 | 1102 | 43 | 243 |
| Median year of prescription | 2006 | 2008 | 2004 | 2005 | 2004 | 2005 | 2001 | 2004 | 2004 |
| Female | 56.2% (434411) | 59.0% (320968) | 49.4% (111825) | 70.3% (843) | 58.5% (165) | 62.5% (35) | 39.6% (436) | 51.2% (22) | 48.1% (117) |
| Age | 56 | 53 | 62 | 56 | 61 | 55.5 | 57 | 57 | 57 |
| CAD | 0.1% (1063) | 0.0% (225) | 0.4% (829) | 0.2% (2) | 0.0% (0) | 0.0% (0) | 0.6% (7) | 0.0% (0) | 0.0% (0) |
| CBS | 0.2% (1382) | 0.0% (271) | 0.5% (1095) | 0.2% (2) | 0.4% (1) | 0.0% (0) | 1.1% (12) | 0.0% (0) | 0.4% (1) |
| CVD | 1.5% (11861) | 0.9% (5028) | 3.0% (6760) | 1.3% (15) | 3.5% (10) | 0.0% (0) | 4.2% (46) | 0.0% (0) | 0.8% (2) |
| Charlson | 29.0% (224534) | 25.6% (139129) | 37.2% (84203) | 39.2% (470) | 44.0% (124) | 17.9% (10) | 45.7% (504) | 25.6% (11) | 34.2% (83) |
| IMD-2010 | 8 | 8 | 9 | 8 | 10 | 12 | 10 | 11 | 10 |
| Consulation rate | 5.3 (5.0) | 5.0 (4.8) | 6.0 (5.4) | 8.4 (7.9) | 7.3 (6.1) | 4.5 (3.0) | 6.7 (5.6) | 8.7 (6.1) | 7.1 (6.6) |
| Alcohol (ever) | 84.3% (652287) | 84.8% (461420) | 83.2% (188501) | 80.3% (963) | 81.2% (229) | 82.1% (46) | 81.5% (898) | 76.7% (33) | 81.1% (197) |
| Smoking (ever) | 48.0% (371158) | 44.9% (244324) | 55.3% (125258) | 52.6% (631) | 57.4% (162) | 53.6% (30) | 55.5% (612) | 46.5% (20) | 49.8% (121) |
| BMI | 26.9 (5.2) | 26.5 (5.1) | 27.7 (5.2) | 27.4 (5.6) | 28.1 (5.6) | 28.8 (5.1) | 29.0 (5.2) | 28.4 (5.6) | 27.0 (5.7) |
| PAD | 0.5% (4039) | 0.3% (1746) | 1.0% (2272) | 0.5% (6) | 0.7% (2) | 0.0% (0) | 1.1% (12) | 0.0% (0) | 0.4% (1) |
| Hypertension | 15.2% (117630) | 11.2% (60779) | 24.8% (56237) | 15.9% (191) | 25.2% (71) | 28.6% (16) | 26.1% (288) | 20.9% (9) | 16.0% (39) |
| Stopped | 5.7% (44439) | 0.0% (0) | 19.2% (43540) | 51.8% (621) | 16.7% (47) | 16.1% (9) | 11.8% (130) | 37.2% (16) | 31.3% (76) |
| Added | 1.3% (9901) | 0.0% (0) | 4.2% (9462) | 3.3% (40) | 18.8% (53) | 7.1% (4) | 22.8% (251) | 9.3% (4) | 35.8% (87) |
| Switched | 0.8% (5890) | 0.0% (0) | 2.2% (5086) | 11.2% (134) | 36.9% (104) | 58.9% (33) | 41.7% (460) | 48.8% (21) | 21.4% (52) |
| Other drug within 5yrs | 1.7% (13363) | 0.0% (0) | 5.4% (12264) | 11.5% (138) | 49.3% (139) | 58.9% (33) | 57.6% (635) | 53.5% (23) | 53.9% (131) |

The proportions of participants with missing covariate information were comparable to those presented in the anti-hypertensives paper.

* Full covariate information was available for 773387 participants (100%).
* IMD 2010 score, a proxy for socioeconomic position that is measured as twentiles with 1 indicating the least deprived and 20 indicating the most deprived, was missing for 0 participants (0%).
* Alcohol status was missing for 0 participants (0%).
* Smoking status was missing for 0 participants (0%).
* BMI, or a calculated BMI from height and weight measurements, was missing for 0 participants (0%).

Table 1 shows the proportion of participants receviving each drug class who subsequently stoppped (greater than 6 months between last prescription and end of data), added (second drug prescribed before last prescription for the index\_drug) or switched (second drug prescribed after last prescription for the index\_drug).

Note: the discrepancies between the number of participants in the table of characteristics and that displayed in the forest plot is due to 90 participants having a diagnosis date prior to the index date (84 in the control group and 6 in the statin group).



The summary results of the Cox proportional hazards models with time varying treatment and adjustment for baseline covariates for any dementia outcome.

Overall, the analysis indicated that treatment with any lipid-regulating agent was associated with an increased HR of dementia, consisent across all dementia sub-types.

In terms of baseline confounders, the largest attenuation was seen on adjustment for age.

Table 2: Cohort 2 - Results from Cox proportional hazards regression of any dementia diagnosis on treatment with any lipid-regulating agent vs no treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Analysis | Covariates | HR | Std Error | P-value | Upper 95%CI | Upper 95%CI |
| Time-varying treatment | none | 1.765 | 0.0103 | 0 | 1.730 | 1.801 |
| Time-varying treatment | age/sex | 1.194 | 0.0103 | 0 | 1.170 | 1.218 |
| Time-varying treatment | full | 1.190 | 0.0154 | 0 | 1.155 | 1.227 |
| Time-varying treatment | NA | 1.208 | 0.0173 | 0 | 1.167 | 1.249 |

For the analyses above, the following baseline covariates were adjusted for: sex, age, charlson, Index multiple deprivation, consultation rate, alcohol (ever), smoking (ever), BMI, cardiovascular disease, coronary bypass surgery, coronary artery disease, peripheral arterial disease, and hypertension. In analyses with time-varying covariates, a participants’ cardiovascular disease, coronary bypass surgery, coronary artery disease, peripheral arterial disease, and hypertension status was allowed to vary over time.

## Mendelian randomization analysis

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# Discussion

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# Conclusions

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## Supplementary tables and figures

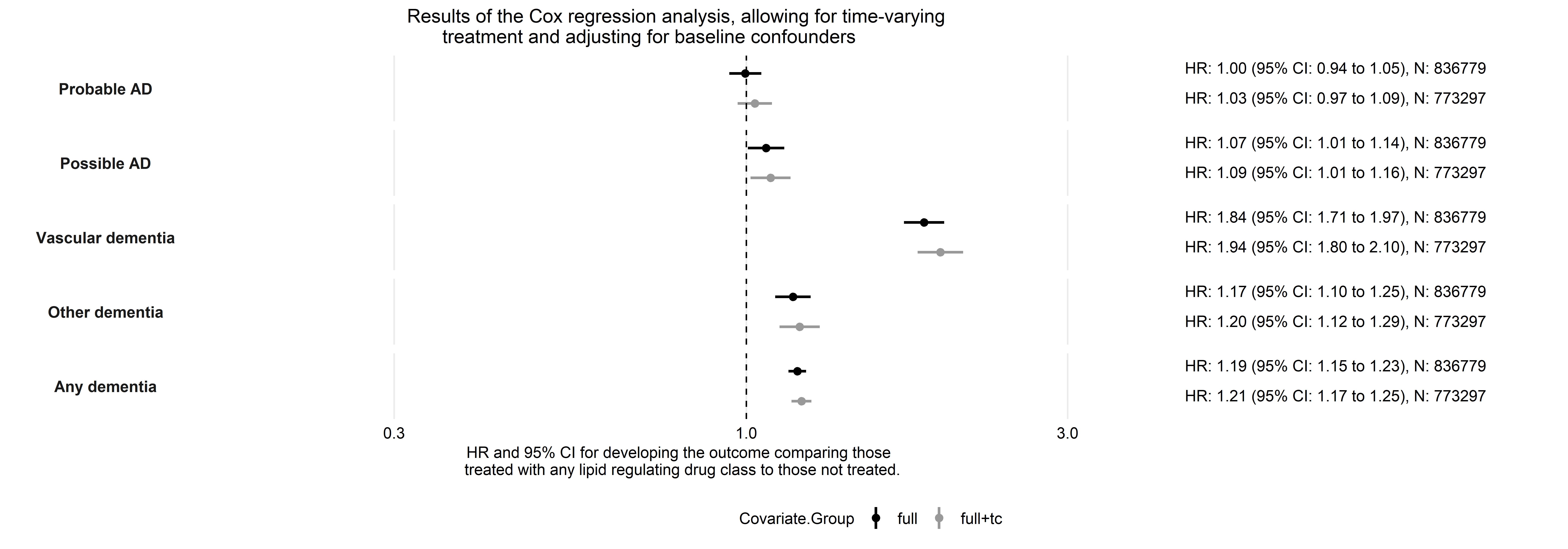


Table 3: Cohort 2 - Results from a time-varying Cox proportional hazards regression model comparing each drug with the control group. The following baseline covariates were adjusted for: sex, age, charlson, Index multiple deprivation, consultation rate, alcohol (ever), smoking (ever), and BMI. The following covariates were allowed to vary over time: Cardiovascular disease, coronary bypass surgery, coronary artery disease, peripheral arterial disease, and hypertension

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Drug | HR | Std Error | P-value | Upper 95%CI | Upper 95%CI | Number of participants |