

# Sex and APOE Genotype Differences Related to Statin Use in The Aging Population

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## Research

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# Abstract

**Background.** Significant evidence suggests that the cholesterol-lowering statins can effect cognitive function, and reduce the risk for Alzheimer's disease and dementia. These potential effects may be constrained by specific combinations of an individual's sex and Apolipoprotein E (APOE) genotype.

**Methods.** Here we examine data from 252,327 UK BioBank participants, aged 55 or over, and compare the effects of statin use in males and females. We identified that in this population, males were older, had a higher level of education, better cognitive scores, higher incidence of cardiovascular and metabolic diseases, and a higher rate of statin use.

**Results.** We observed that males and those participants with an APOE4 (E4 variant of APOE) positive genotype had higher probabilities of being treated with statins; while participants with an Alzheimer's diagnosis had slightly lower probabilities. We found that use of statins was not significantly associated with overall higher rates of survival. However, when considering the interaction of statin use with sex, the results suggest higher survival rates in males treated with statins. Finally, examination of cognitive function indicates a potential beneficial effect of statins, however this is limited to APOE4 positive genotypes.

**Conclusions.** Our evaluation of the ageing population in a large cohort from the UK BioBank confirms sex and APOE genotype as fundamental risk stratifiers for Alzheimer's disease and cognitive function, furthermore it extends them to the specific area of statin use, clarifying their specific interactions with treatments.

## 1. Background

The aging of the population has been recognized as a key policy issue worldwide. The proportion and absolute number of older people are increasing dramatically: by 2040, nearly one in seven people is projected to be aged over 75 years (1). Eurostat projections suggest there will be 66.1 million people aged 80 years and over in the European Union by 2080 (2). These trends will have a major impact on public spending. In the UK, the Office for Budget Responsibility forecasts total spending to increase from 33.6–37.8% of GDP between 2019 and 2064 – equivalent to current £79 billion – due mainly to the ageing population (3). In the US, Medicare expenditures are projected to rise to 6–9% of GDP with predicted strain on Federal budget and national economy (4). The burden of these expenditures will mainly affect healthcare systems as much of health care expenditures are incurred in last years of life. A crucial point for policy development is whether extended life span is matched by health span.

Healthy ageing has been defined as “the process of developing and maintaining the functional ability that enables well-being in older age” (1). It focuses on the perspective of elderlies' trajectory of functioning rather than the only disease they are experiencing at a single point in time, and it includes the concept of intrinsic capacity, which is the composite of all the physical and mental capacities of an individual. Healthy life expectancy, which indicates a reduction of years spent in ill-health, is not keeping pace with increasing life expectancy. This suggests an increasing prevalence of chronic age-related conditions with long duration preclinical phases such as Alzheimer's (3).

Sex differences in longevity are well documented and feature in many species in addition to humans (5–7). While it is common for women to live longer than men, the magnitude of the difference in longevity differs across cultures and is modifiable by environmental factors and the difference in life span is declining in developed nations (8).

There is mounting evidence to suggest that statins, used to regulate cholesterol levels, may effect cognitive function, reducing the risk for older age associated Alzheimer's disease (AD) and dementia (9–13). Nevertheless, clinical trials evaluating the effects of statins in AD patients have largely failed, resulting with no significant therapeutic benefit (14–17). Sex differences, as well as the effects of the genotype of the cholesterol transporter and AD risk factor Apolipoprotein E (APOE), are well documented in statin drug response (18–20). In a recent examination of the association between statin

use and the incidence of AD among Medicare beneficiaries it was found that reduction in Alzheimer disease risk varied across statin molecules, sex, and race/ethnicity (21).

A major resource that can enable investigations in ageing populations is the UK BioBank (22), aimed at improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening diseases. The UK BioBank has recruited 500,000 people aged between 40–69 years (with over 200,000 of these over the age of 60) in 2006–2010 from across the United Kingdom. All subjects have provided extensive demographic and health-related information as well as biologic samples and are continually followed. Further, UK Biobank is linking to a wide range of electronic health records such as death, hospital episodes and general practice.

The aims of this study are (i) to assess differences in treatments in the aging population and identify potential stratifiers for greater beneficial effects of statins; and (ii) to evaluate the effect of statin use in the aging population on survival, AD incidence and cognitive decline. Our study design and analytical strategy is described in Fig. 1

While previously the cost-effectiveness of a polypill, including simvastatin, to prevent cardiovascular diseases has been assessed in the UK BioBank cohort (23), to the best of our knowledge our work is the first to report on statin use within the UK BioBank's aging population.

## 2. Methods

### 2.1 Population and data

From the entire UK BioBank cohort, individuals aged 55 and over at recruitment (baseline) with determined APOE genotype were selected.

Baseline variables (age at recruitment and sex) were captured from UK BioBank database. Social-economic status of participants was assessed using the Townsend deprivation index. Each participant is assigned a score corresponding to the output area in which their postcode is located. To assess individuals' education level, we extracted data from the Education qualifications variable indicating if the individual have a College or university degree, as in (24).

### 2.2. Cognitive measures

An extensive description of the cognitive function tests administered to UK BioBank participants is provided by Lyall et al (25), as is a report on missingness of the cognitive scores among individuals and their intra-variability over time.

From these scores, the Reaction Time (RT) test is used to assess reaction time, based on 12 rounds of the card-game 'Snap' (26). Participant are shown two cards at a time; if both cards are the same, they are instructed to press a button-box as quickly as possible. The score on this task is the average response time in milliseconds across the 12 rounds.

Longitudinal studies of cognitive measures based on UK BioBank are rare. A recent study (27) used the RT to assess cognitive decline relationship with alcohol consumption. As shown in (25) RT scores got worse over time, while other scores related to Visual/Numeric memory (Pair Test) and reasoning (Fluid Intelligence) improved. Differently from these previous studies, which use measurements at the baseline and at the first follow-up, we use three time points: baseline and two follow-up visits. And, similarly to previously demonstrated patterns, RT measures worsened over time, while Pair Test and Fluid Intelligence scores improved. On the basis of these findings we focus on the use of RT scores as proxy for cognitive impairment where increasing values of reaction time indicates a worsening in cognitive performances.

### 2.3 Disease diagnoses

Referring to the work in (21), which studied the risk of Alzheimer disease in relation to statin use, we included the diagnoses of the following prevalent conditions: Alzheimer's disease, dementia, cardiovascular (acute myocardial infraction, atrial

fibrillation, acute cerebrovascular disease, coronary atherosclerosis, angina and hypertension) and metabolic diseases (diabetes, disorders lipid metabolism). We used the ICD10-CM codes in the UK BioBank and applied the disease Clinical Classifications Software (CSS) (28) on identified diagnosis codes to aggregate them into single-level disease categories. Single and multilevel categories, and corresponding code sets, are provided in Supplementary file 1.

## 2.4 Determination of drug exposure

The medications category of the UK BioBank contains data on type and number of regular treatments taken by each individual. The data are obtained through a verbal interview by a trained nurse and coded via READ codes. We built a code set for each of the medication groups of interest (reported in Appendix A). These medications have previously been linked to cognitive impairment and included statins, non-statin cholesterol lowering drugs, AD medications, antidepressants, non-steroid anti-inflammatory drugs (NSAIDs), estrogens, diabetes medications, vitamin E, omega-3 and derivatives, and medications for long-term asthma management.

## 2.5 Determination of APOE genotype

In UK BioBank the APOE genotype is directly genotyped via the SNPs rs429358 and rs7412. Values are for either of the two SNPs were available for 299,627 participants; of these 47,299 participants were missing a value for one of the two SNPs and were therefore excluded. For further analyses, a total of 252,327 participants were included. APOE genotype missingness is due to UK Biobank enrollment procedures (i.e. participants recently enrolled for which the information is not available yet) or technical issues, therefore we assume is Missing Completely at Random.

## 2.6 Statistical analyses

We compared and contrasted the population as stratified by sex and APOE  $\epsilon$ 4 genotype. To test for significant differences among the 4 groups (Female APOE4, Female non- APOE4, Male APOE4, Male non- APOE4) we applied Kruskal-Wallis for continuous variables, and chi-square for categorical ones.

We further compared APOE4 carriers within females and males using t-test and chi-square. Cochran-Mantel-Haenszel test was used performed a stratified analysis considering the population distributions in Ethnicity strata.

The results were corrected for multiple testing. All analyses were computed using R version 3.2.3. Results are presented as the main effect with a 95% confidence interval. A significance level of 5% was used for main inferences.

In order to study drug exposure, while minimizing the effects of possible confounders and including relevant stratifiers, we applied propensity scoring to assess the comparability of case mix and, on this basis, created matched data sets for each of the drug categories.

Given the definition of propensity scores (i.e. the probability of being treated) this step allows us to compare the score in females and males, thus assessing relevant differences in treatments between the sexes. To adjust for different distributions of characteristics across treated groups (i.e. age, social-economic status, education level and relevant diagnoses for each drug), patients were stratified based on their propensity of being treated with a specific drug. It is important to note that sex is not included as a potential confounder, as the aim of this analysis was to study its correlation with treatments, and then use it as stratifier for the following analyses.

For each drug, we derived a sample matched (with a 1:1 ratio) on the propensity score and compared the probability of being treated (i.e. propensity score itself) between females and males with t-tests. Analyses were performed using the functions `matchit` and `match.data` from the `MatchIt` R package (29).

To further study statins exposure differences in the aging population, we applied a logistic regression model and conditional inference tree (to visually illustrate associations between the selected covariates and response) on the matched

cohort (where the propensity score is computed based on treatment with statins). In both the models we assess the exposure to statins on the basis of covariates not included in the propensity score analyses (i.e. sex, AD, dementia, and APOE4 genotype). We used the “rpart” and “rpart.plot” function of the rpart package (30).

Once we assessed the probability of being treated with statins and identified key stratifiers, we evaluate the effect of statins on specific outcomes (i.e. survival, AD prevalence and cognitive decline) in the matched cohort.

To examine the effect of statin use on survival in the aging population, death records captured by UK BioBank were used for this analysis. We used baseline measurements to build a survival model, left-censored at baseline. Right-censoring was applied at the last follow-up date or data of death (if death occurred). Survival was studied with a Cox regression model adjusted by sex, APOE genotype, Alzheimer’s, and dementia diagnosis. We perform the analysis with the “coxph” function of the “survival” package (31).

For the assessment of longitudinal cognitive patterns in relation to statin use we included individuals who had at least two measurements (from 2 visits) including baseline assessment. This selection of participants may have introduced some bias but was essential to determining slope of change in cognitive measures.

To test for differences in the rate of change of the cognitive measures between statin-user and non-user groups over the entire follow-up period we used a linear mixed-effects model (using the lme4 package (32)) including the visit (time) effect, interaction terms with statins treated/non-treated groups and adjusted for gender and APOE genotype as relevant stratifiers. To further study intra-individual variability of RT over years we compute the slope of RT over time as the difference of the measure at follow up and the baseline divided by the time in-between the two measures (eq.1). Higher Slope.yrs values indicate greater deterioration of cognitive function in time, while negative values indicate improvements.

$$(eq.1) \quad Slope.yrs = \frac{RT(fup) - RT(baseline)}{Time.yrs(fup) - Time.yrs(baseline)}$$

To examine the potential effect of statin use on prevalence of Alzheimer’s disease in the UK BioBank population, we conducted a cross-sectional analysis on individuals who were diagnosed with AD at baseline and were APOE genotyped in the matched data set. Longitudinal information was not available for these participants, likely due to loss of follow-up or drop out from the study (after initial, baseline evaluation). Therefore, we studied Alzheimer’s prevalence with a multivariate logistic regression model with statin use, APOE genotype, and sex as interaction terms.

## 3. Results

### 3.1 The UK Biobank aging population

From the entire UK BioBank cohort of more than 500,000 individuals, 252,327 who were aged 55 or over at recruitment (baseline) had a determined APOE genotype and were selected for our investigations (Table 1). Of these 14,523 (4.717%) had data available from their first follow-up visit and 2,677 (0.87%) had data available from baseline, first and second follow-up visits.

We found no differences in the population distribution in the four main classes (defined by sex and APOE genotypes), nor where there any difference when stratified by ethnicity.

A comparison of females (n=136,665) and males (n=115,662) revealed that the two groups differ in terms of age, education level, cognitive measures, disease diagnoses, and statin use, but not for the Townsend deprivation index or the incidence of Alzheimer Diseases.

The data illustrates that in the selected population, males are older, generally have a higher level of education, better cognitive scores, higher incidence of all the cardiovascular and metabolic diseases included in the analysis, and they have a higher rate of statins use. We further compared between males and females stratified by APOE genotypes (carriers vs. non-carriers of the APOE4 allele). In both females and males, statistically significant differences were found for several disease diagnoses, including Alzheimer and Dementia, and in use of different statins, excluding pravastatin in males. As for cognitive measures at baseline, only RT was found statistically significant different in both females and males when comparing between APOE4 carriers and non-carriers.

### 3.2 Drug exposure in the ageing population

To assess drug exposure in the aging population, datasets matched via Propensity Score (PS) for each drug were created (Table 2). We observed significant differences in drug exposure between females and males, as also depicted in Figure 2. Females are less likely to be treated with antidepressants, asthma, diabetes drugs, and non-statin lipid lowering drugs; they are more likely to be treated with non-steroidal anti-inflammatory drugs and Omega 3.

We were specifically interested in examining statin exposure differences, and so applied a logistic regression model and conditional inference tree to assess the exposure in the matched dataset (Supplementary Table 1) on the basis of features not included in the propensity score analyses (i.e. sex, AD and dementia diagnoses, and APOE4 genotype – indicated in Supplementary Table 1 as non-matched).

Based on the regression model, males (z-value=51.2, p-value < 2e-16) and participants with an APOE4 positive genotype (z-value=10.6, p-value < 2e-16), have a higher probability of being treated with statins. Interestingly, in this population, participants with an AD diagnosis were slightly less likely to be treated with statins (z-value=-3.0, p-value = 0.00246). Models output are reported in Supplementary Table 2.

Taking a second approach to better illustrate statin exposure differences by stratifiers, we apply recursive-partitioning and present the results in the form of a logical tree structures (Figure 3). Treatment with statins is stratified on the basis of sex, APOE genotype and degenerative diseases. However, the model suggests that treatment is stratified on the basis of APOE genotype in males (nodes 14 and 15), but not in female participants. Tree models also provide lists of rules, which summarize the branch path to each final node and its predicted probability. Within our model, the rule associated with the lowest probability of being treated (0.21) is the one including females without a diagnosis of AD (node 4); while the one with the highest probability of being treated (0.63) is that which includes males diagnosed with AD or dementia and who have an APOE genotype (node 31).

### 3.3 Effects of exposure to statins

To examine the effect of statin use on survival in the aging population, death records captured by UK BioBank were used for this analysis. We performed the following analysis on the dataset matched on the statin propensity score, thus including as covariates sex, APOE genotype, Alzheimer's, and dementia diagnoses, as well as their interactions with statin treatment.

The matched data set included a total of 6622 death events (3170 in statin users and 3452 in non-users). The multivariate cox regression analysis (Table 3) revealed that use of statins was not significantly associated with overall higher rates of survival (p-value = 0.206). On the other hand, when considering the interaction of statin use with sex, the results suggest higher survival rates in males treated with statins.

As suggested by our analyses of statins exposure, individuals differ in prevalence of statin use on the basis of strata defined by sex and APOE genotype. Here we examined whether differences in use of statins have an effect on changes in RT, where higher RT scores indicate worse cognitive function.

To assess changes in cognitive patterns, as measured by RT, in relation to statin use, we included individuals who had at least two measurements (from 2 visits) following baseline assessment. The average length of time (days) between baseline and first follow-up was  $1565.64 \pm 343.2$ , and  $962.66 \pm 288.6$  between first and second follow-up visits, respectively. A total of 3,877 individuals from the matched cohort had available RT measures (milliseconds) data at least two visits (Supplementary Figure 1)

A linear mixed effects model was used to test for differences in the rate of change in the RT measures over the entire follow-up period (3 time points) in the statins matched dataset. The model includes a random effect term indicating variation over time in each subject (Time from baseline | Subject), and adjusted for sex, APOE genotype and their interactions with statins treatments (Table 4). Changes in reaction time measures were significantly associated with time from baseline (scores worsened in time, as previously described (25)) as well as sex; males had worse performance over time. Statistically significant differences ( $p=0.03$ ) were found in the change in reaction time between statin users and non-users when stratified by APOE genotype.

Figure 4A illustrates RT scores at each of the available time points (0=Baseline, 1=First Visit, 2=Second Visit) in statin users (red) and non-users (grey) in each of the strata suggested by the model (male and female, and APOE4 carriers and non-carriers). As suggested by the mixed effect model (Table 4), significant differences are observed only when the interaction between treatment and APOE4 genotype is considered. In general, statin users have worst RT score during the whole observation period, but these differences are reduced in APOE4 carriers. Specifically, in male APOE4 carriers, statin users and non-users demonstrate substantial overlap of RT scores in time and, while not statistically significant, they are the only strata where RT is higher in non-users (mean=6.33, sd=0.1) than in user (mean=6.32, sd=0.1) at baseline.

We tested the differences in RT Slope.yrs between statin users and non-users in each of the strata (see Figure 4B). Larger slopes indicate faster deterioration of cognitive function in time. No significant differences were seen. However, as already suggested by Figure 4B, different behaviors in deterioration can be seen: in females with an APOE4 carrier genotype, statin non-users deteriorate faster (mean RT slope=6.24 (mmsec)/years) than statin users (mean RT slope=6.02 (mmsec)/years); this is unlike males without an APOE4 carrier genotype, where statin non-users deteriorate slower (mean RT slope=4.70 (mmsec)/years) than users (mean RT slope=4.77 (mmsec)/years).

Our results therefore indicate that statins may have a beneficial effect on cognitive functions, however this may be limited to specific combinations of sex strata and APOE4 genotypes.

### 3.4 Statin use and Alzheimer's disease

To examine the potential effect of statin use on prevalence of Alzheimer's disease, a multivariate logistic regression model including statin use, APOE genotype, and sex as interaction terms found that, as expected, APOE4 carriers demonstrate an increased risk for AD (z-value = 11.05,  $p < 2e-16$ ). More interestingly, while statin users have increased risk of AD (z-value = 3.76,  $p = 0.00017$ ), APOE4 carriers, reported to be using statins, demonstrate a decreased risk for AD (z-value = -1.77,  $p = 0.07$ ), though marginally significant. The full models' outputs are reported in Supplementary Table 3.

## 4. Discussion

We have previously demonstrated that statins have greater beneficial effects on cognitive function in APOE4 homozygotes (9). Further, Zissimopoulos et al (21) have demonstrated, using Medicare patients' records, that a reduction in Alzheimer disease risk is associated with statin use and varies across different statins, sex, and ethnicity. Using data from the UK BioBank we aimed to further examine potential effects of statin in the aging and AD populations by stratifying by sex and APOE genotype.

Our results have consistently supported sex differences related to statin use in the ageing population. Most strikingly, when we examined statin exposure differences in the ageing population while allowing for multilevel stratification, we found significant differences in the strata which contribute to prevalence of statin use. Specifically, APOE genotype is correlated to differences in rates of treatment with statins in males but not in females. Multivariate survival analysis revealed that changes in survival are associated to the use of statins only when accounting for the interaction with sex strata. Further, analysis of cognitive measures in statin users vs. non-users suggests that males with an APOE4 genotype may benefit more from use of statins, however this analysis was somewhat limited. We also found that participants with an AD diagnosis were slightly less likely to be treated with statins; this may be due to reverse causation, where statins are more likely prescribed to patients who are not cognitively impaired and would adhere to treatment. In accordance with previous findings (9) we found that APOE4 carriers, reported to be using statins, demonstrate a decreased risk for AD (though not statistically significant).

## 5. Limitations

One of the most significant limitations is that the cognitive measures available for analysis in the UK Biobank data may not fully capture cognitive changes over time in this non-clinically impaired population. While reaction time has been used successfully to assess cognitive impairment in ageing and dementia populations (33–35), the finer changes related to statin use may be better captured with more robust, specific, diagnostically-designed measures such as Mini Mental State Examination (36) or the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog) (37). Additionally, we could not conduct longitudinal analysis of change in cognition over time in the AD cohort as these data were not available. This is most likely due to drop out, as individuals diagnosed with AD are less likely to follow-up with a study such as the UK BioBank. Nevertheless, our analyses revealed that statin use in APOE4 carriers, decreases the risk for AD, in alignment with findings from previous studies (9). UK BioBank data has several potential biases, some are general ones such as the enrollment of a mostly white population, with higher socioeconomic status, others are related to this specific study, including possible selection biases, such as higher rates of depression in females.

## 6. Conclusions

To conclude, our evaluation of the ageing population in large-scale cohort from the UK BioBank has identified important sex differences related to statin use. Together, our results suggest that patient stratification that includes APOE genotype and consciousness of sex bias could significantly reduce risk of Alzheimer’s disease in both men and women.

## Abbreviations

AD  
Alzheimer’s disease. APOE:Apolipoprotein E. APOE4:genotypes carrying the E4 variant of Apolipoprotein E. RT:Reaction Time. CSS:Clinical Classifications Software. NSAIDs:non-steroid anti-inflammatory drugs. PS:Propensity Score.

## Declarations

### Ethical Approval and Consent to participate

This research has been conducted using the UK Biobank Resource under Application Number 19923 “A precision medicine approach for treatment and prevention of Alzheimer’s disease using statins.” UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC), which covers the UK.

### Consent for publication

All participants have previously provided consent for UK Biobank data and samples to be used for research.



## Availability of data and materials

The data that support the findings of this study are available from UK Biobank. Restrictions apply to the availability of these data, which were used under the application 19923 license for the current study, and so are not publicly available.

## Competing interests

The authors have no financial conflicts of interest.

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## Authors’ contributions

AD performed the analyses included in this manuscript and wrote the manuscript draft. AD, NG, NP, RDB designed and developed the study. All authors contributed to the writing and revision of the manuscript.

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## Tables

**Table1.** For comparison among 4 groups (female and male with/without APOE4) Kruskal-Wallis and chi-square tests were applied to test for significance. For the comparison of APOE4 carriers within females and males t-test and and chi-square were used. We corrected the results for multiple testing using  $\alpha=0.05/66=0.00076$ , where 66 is the number of test performed. ns  $p\text{-val}>0.0007$ , \*  $p\text{-val}\leq 0.0007$

Sex	Female		<i>p-val</i>	Male		<i>p-val</i>	<i>p-val</i>
APOE4 Carrier	NO	YES	<i>APOE4 in Female (YES/NO)</i>	NO	YES	<i>APOE4 in Male (YES/NO)</i>	<i>Comparing Gender and APOE carrier</i>
<b>Number of patients</b>	101366	35299		85763	29899		0.905
<b>Ethnicity (%)</b>							
Asian	1507 (1.5)	282 (0.8)		1751 (2.0)	384 (1.3)		0.065
Black	944 (0.9)	471 (1.3)		692 (0.8)	361 (1.2)		0.604
Chinese	308 (0.3)	59 (0.2)		173 (0.2)	33 (0.1)		0.985
Mixed	418 (0.4)	151 (0.4)		288 (0.3)	100 (0.3)		0.791
Other ethnic group	754 (0.7)	201 (0.6)		538 (0.6)	139 (0.5)		0.801
Not Known	316 (0.3)	110 (0.3)		424 (0.5)	163 (0.5)		0.490
White	97120 (95.8)	34025 (96.4)		81897 (95.5)	28719 (96.1)		0.919
<b>Mean age at Recruitment (SD)</b>	61.93 (4.1)	61.9 (4)	0.206	62.22 (4.1)	62.24 (4.1)	0.344	<0.0007*
<b>University/College Degree (%)</b>	40586 (40)	9377 (26.6)	0.007	40763(47.5%)	9465(31.7%)	0.084	<0.0007*
<b>Townsend deprivation index (SD)</b>	-1.55 (2.9)	-1.6 (2.9)	0.004	-1.52(3)	-1.51(3)	0.701	0.645
<b>Cognitive measures (SD)</b>							
<b>Fluid Intelligence</b>	5.81 (2.1)	5.83 (2)	0.261	6.09 (2.2)	6.08 (2.2)	0.623	<0.0007*
<b>Paris test – 1<sup>st</sup> round</b>	0.65 (1.3)	0.66 (1.3)	0.356	0.57 (1.3)	0.58 (1.3)	0.089	<0.0007*
<b>Paris test – 2<sup>nd</sup> round</b>	4.46 (3.4)	4.48 (3.5)	0.151	4.51 (3.7)	4.45 (3.6)	0.021	<0.0007*
<b>Reaction Test</b>	590.86 (122.3)	589 (119.2)	0.019	570.07 (119.5)	572.24 (120.9)	0.003	<0.0007*
<b>Diagnoses (%)</b>							
<b>Alzheimer</b>	110 (0.1)	116 (0.3)	<0.0007*	112 (0.1)	106 (0.4)	<0.0007*	0.192
<b>Dementia</b>	220 (0.2)	154 (0.4)	<0.0007*	397 (0.5)	175 (0.6)	<0.0007*	<0.0007*
<b>Acute Myocardial Infraction</b>	1578 (1.6)	444 (1.3)	<0.0007*	5450 (6.4)	1449 (4.8)	<0.0007*	<0.0007*
<b>Atrial Fibrillation</b>		1381 (3.9)	0.144	10323 (12)	2476 (8.3)	0.073	<0.0007*

<b>Hypertension</b>	5717 (5.6)	7685 (21.8)	0.441	36681 (42.8)	8815 (29.5)	<0.0007*	<0.0007*
<b>Diabetes</b>	32939 (32.5)	1492 (4.2)	0.003	11025 (12.9)	2375 (7.9)	0.002	<0.0007*
<b>Acute Cerebrovascular Disease</b>	7009 (6.9)	233 (0.7)	0.537	1760 (2.1)	460 (1.5)	0.018	<0.0007*
<b>Coronary Atherosclerosis</b>	1056 (1)	1675 (4.7)	<0.0007*	19270 (22.5)	5333 (17.8)	<0.0007*	<0.0007*
<b>Disorders Lipid Metabolism</b>	6651 (6.6)	3616 (10.2)	<0.0007*	10855 (12.7)	2849 (9.5)	<0.0007*	<0.0007*
<b>Angina</b>	12057 (11.9)	1502 (4.3)					
	5845(5.8)						
<b>Statin Use (%)</b>	22376 (22.1)	6728 (19.1)	<0.0007*	36020 (42)	9851 (32.9)	<0.0007*	<0.0007*
<b>Simvastatin Use</b>	16180 (16)	4665 (13.2)	<0.0007*	25858 (30.2)	6777 (22.7)	<0.0007*	<0.0007*
<b>Atorvastatin Use</b>	3913 (3.9)	1281 (3.6)	<0.0007*	1135 (1.3)	295 (1)	0.072	<0.0007*
<b>Pravastatin Use</b>	716 (0.7)	224 (0.6)	<0.0007*	1110 (1.3)	397 (1.3)	<0.0007*	<0.0007*
<b>Rosuvastatin Use</b>	844 (0.8)	325 (0.9)					

**Table2.** Comparison among Female and Male of propensity scores in each matched data set. PS values are compared via t-test. \* p-val<=0.05, \*\* p-val<=0.01, \*\*\*p-val<=0.001

<b>Drug</b>	<b>Matched Data (N)</b>	<b>PS in Female Mean (SD)</b>	<b>PS in Male Mean (SD)</b>	<b>p-values</b>
<b>AD medications</b>	152	0.04(0.06)	0.04(0.06)	0.57
<b>Antidepressant</b>	27578	0.06(0.02)	0.07(0.03)	< 0.001**
<b>Asthma</b>	13012	0.02(0.1)	0.03(0.1)	< 0.001**
<b>Diabetes</b>	24554	0.36(0.2)	0.40(0.2)	< 0.001**
<b>Non Statins Lipid Lowering</b>	5164	0.02(0.03)	0.04(0.03)	< 0.001**
<b>NSAIDs</b>	66224	0.137(0.01)	0.135(0.1)	< 0.01*
<b>Omega 3</b>	22340	0.0479(0.009)	0.0475(0.009)	< 0.01*

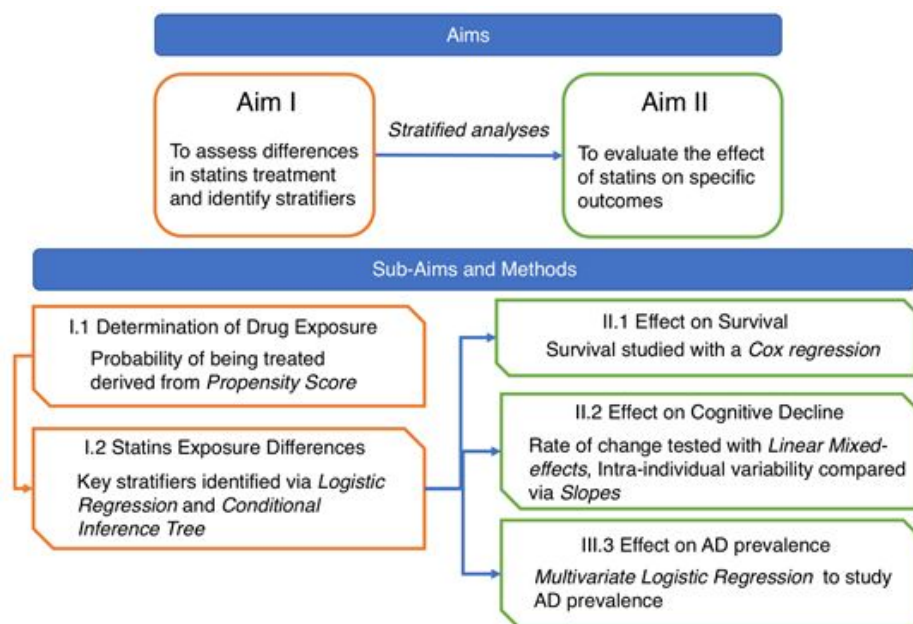
**Table 3.** Results from the Cox regression model of survival. . \* p-val<=0.05, \*\* p-val<=0.01, \*\*\*p-val<=0.001

	Estimate	Standard Error	z.value	p-value
Statin-treated	0.92062	0.0654	-1.265	0.206
APOE4 Carriers	1.14758	0.05871	2.345	0.019*
Sex (Male)	1.7755	0.06404	8.964	< 0.001***
AD Diagnosis	2.34424	0.14309	5.954	< 0.001***
Dementia Diagnosis	6.49512	0.07762	24.104	< 0.001***
APOE4 Carriers: Sex (Male)	0.91895	0.0654	-1.292	0.1962
Sex (Male): Statin- treated	1.1226	0.05223	2.214	0.0268*
APOE4 Carriers: Statin- treated	1.02295	0.06262	0.362	0.7172

**Table 4:** Analysis of Variance Table from linear mixed effect model of the rate of change in reaction time measures between the statin-users and non-users. . \* p-val<=0.05, \*\* p-val<=0.01, \*\*\*p-val<=0.001

	Sum Sq	Mean Sq	NumDF	DenDF	F.value	Pr(>F)
Statin-users (Yes)	0.0058	0.0058	1	3864.1	0.382	0.53675
Time (Follow-up)	4.8107	4.8107	1	4463.5	315.551	<2.20E-16 ***
APOE4 Carriers	0.0007	0.0007	1	3870.9	0.045	0.83219
Sex (Male)	0.5119	0.5119	1	3863.8	33.58	7.39E-09 ***
Statins: APOE4 Carriers	0.0695	0.0695	1	3870.6	4.556	0.03286 *
Statins:Sex	0.0058	0.0058	1	3864.1	0.382	0.53675

## Figures



**Figure 1**

Study aims and analysis flow chart

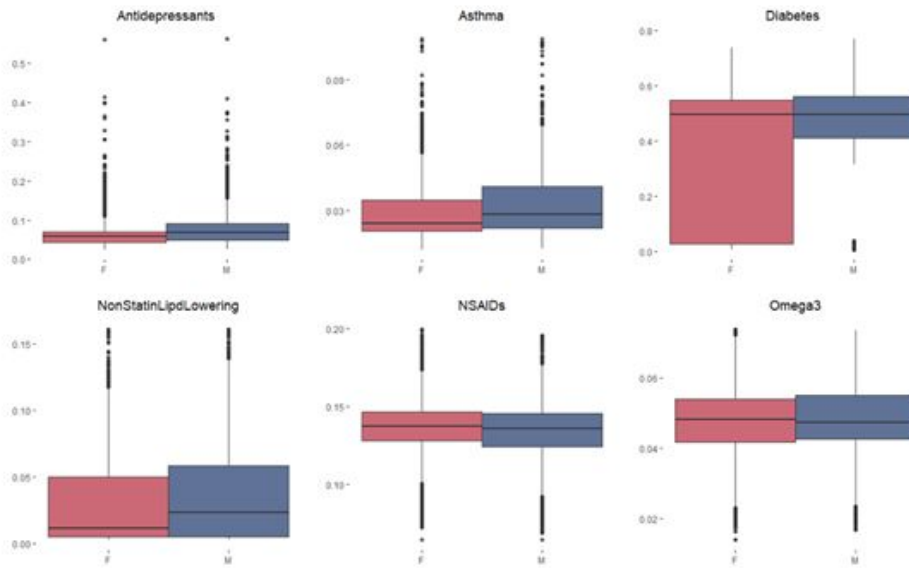


Figure 2

Drug exposure propensity scores in females (red) and males (blue) in the matched data sets.

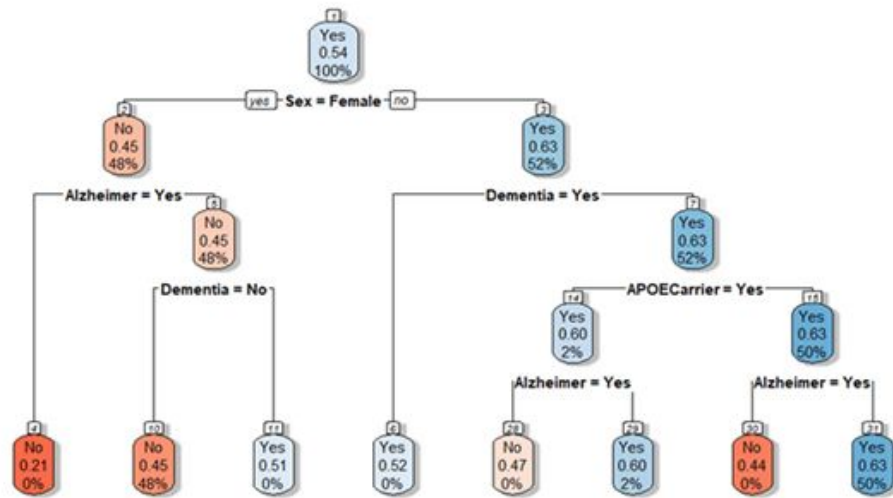
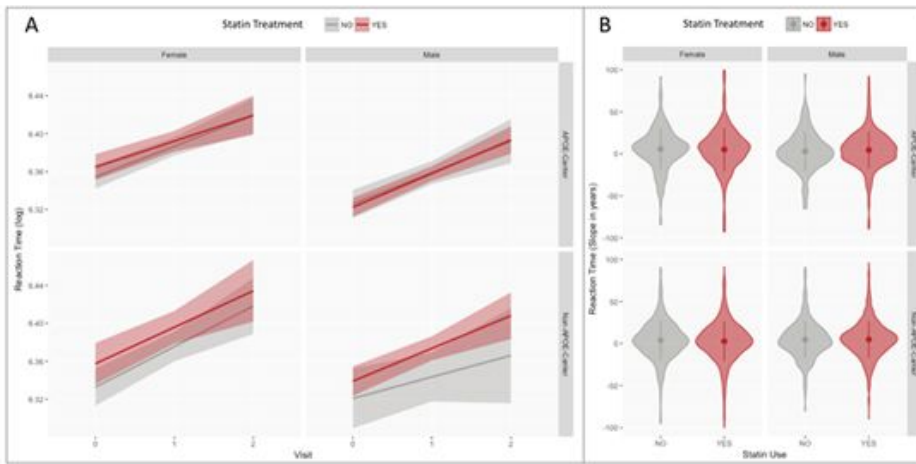


Figure 3

Results of the tree model. Each node shows the predicted class (Yes=treated or No=not treated), the predicted probability of being treated and, the percentage of observations in the node.



**Figure 4**

Comparison of statin users (red) and non-users (grey) in the different population strata. For each of the four strata, the figure reports RT log-transformed scores in time, and the RT Slope.yrs in the observation period.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AppendixSexDifferencesinStatinresponseUKBB.docx](#)