Antidepressant Use and Risk of Dementia and Cognitive Decline

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Abstract

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The causes of late-onset dementia and cognitive decline are not fully understood, and are likely the result of a complex interplay between genetics, environment, and health and lifestyle factors. In light of the devastating personal and economic burden of dementia, targeting midlife factors that contribute to these diseases could lead to important interventions to ameliorate risk and/or delay onset. Depression, a common condition among older adults, has been linked to dementia outcomes in multiple studies. It is unknown whether pharmacological treatment can alter this risk. Treating depression may benefit those at risk of dementia and Alzheimer's disease (AD) by virtue of neurogenic properties, or by altering the pathobiological pathway between depression and dementia. Additionally, non-modifiable genetic risk factors may influence disease outcomes, either directly or through gene x environment interactions. The ε4 variant of the *apolipoprotein E* (*APOE*) gene is the most-studied and well-established genetic risk factor for dementia, and may interact with depression and/or antidepressant medications to influence risk of dementia and cognitive decline. In the following chapters we present an interdisciplinary dissertation project that seeks greater understanding of the epidemiology of pharmaceutical depression management, genetics, and dementia risk in an aging population, as well as ethical considerations for future studies.

The first chapter describes a pharmacoepidemiology study, which measured associations between antidepressant use and dementia and the rate of cognitive decline using a large longitudinal cohort of older adults with biannual cognitive testing and detailed pharmacy records. The second chapter

examines the complex interactions between a known genetic risk variant, the ε4 variant of the *apolipoprotein E* (*APOE*) gene, and depression and antidepressant use in this population. Finally, the last chapter built on the results of the first two chapters to discuss the ethical considerations of genotype-driven recruitment strategies in the context of a research study testing an intervention on individuals with a known risk-conferring gene variant, *APOE* ε4.

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Chapter 1

Antidepressant use and risk of dementia and cognitive decline

Abstract

Background: The purpose of this study was to determine if antidepressants were associated with dementia risk. Effects may differ by antidepressant class, as some have known anticholinergic activity (tricyclic antidepressants (TCAs) and paroxetine), which may increase risk, while long-term effects of selective serotonin reuptake inhibitors (SSRIs) are unknown.

Methods: The parent study, Adult Changes in Thought (ACT), is a prospective population-based cohort in an integrated health care delivery system. Initial recruitment occurred from 1994-1996 and 2000-2003, followed by continuous enrollment since 2004. The cognitive abilities screening instrument (CASI) was administered every two years to screen for dementia and was used to examine cognitive trajectory. For these analyses, eligible participants had at least 10 years of enrollment in the health care system at baseline (N=3342, data through December 31, 2013). Primary exposures were selective serotonin reuptake inhibitors (SSRIs) (paroxetine vs. others), tricyclic antidepressants (TCAs), and serotonin antagonist and reuptake inhibitors (SARIs). All other antidepressant classes were grouped together and adjusted for in the models. Computerized pharmacy dispensing data were used to ascertain cumulative medication exposure, defined as total number of standardized daily doses (TSDDs) dispensed over a 10-year period (a rolling window from ACT cohort entry through end of follow-up). Exposure in the most recent year was excluded to avoid use related to prodromal symptoms. Dementia risk was analyzed using Cox proportional hazards models adjusted for age via the time axis, and for demographic characteristics, health behaviors, and health status. Analysis of cognitive trajectory used linear regression models with generalized estimating equations.

Results: During a mean follow-up of 7.9 years, 864 participants (25.9%) developed dementia (699 Alzheimer's disease). An antidepressant was used by 48.6% of the study population during the study period. Paroxetine use was associated with increased risk of dementia at all TSDD categories (HRs 1.46-2.06) compared to no use, although the confidence interval crossed 1 for some categories. Other SSRIs, TCAs, and SARIs were not significantly associated with increased risk of dementia. Results were similar

for Alzheimer's disease. High non-paroxetine SSRI use (>1095 TSDDs) was associated with a faster rate of cognitive decline than non-users (-0.05 CASI points/year difference between non-users and users, 95% CI, -0.010, -0.004; interaction p-value = 0.032). Other antidepressants were not associated with faster or slower rates of cognitive decline compared to non-users.

Conclusions: Paroxetine use, but not other antidepressant use, was associated with higher risk of dementia and Alzheimer's disease, even in participants with 90 or fewer TSDDs. Although this association may not be causal due to confounding by indications associated with premorbid symptoms, it is plausible given that other anticholinergic medications have been associated with dementia risk. These results reinforce the need to increase awareness among health care professionals of the risks of certain medications for older adults.

Introduction

Antidepressants are among the most commonly prescribed medications in the US [1]. Approximately 11% of Americans 12 years and over were taking an antidepressant between 2005 and 2008, with up to 60% of Americans taking antidepressants for two years or longer [2]. Older adults (>50 years) had the highest rate of use at approximately 15% [1,2], though little is known about the long-term effects of antidepressant treatment on cognitive outcomes and risk of dementia and Alzheimer's disease (AD).

The effects of antidepressant medications on dementia risk is of particular interest, as depression itself has been characterized as a risk factor for dementia in multiple longitudinal studies [3–9]. The reasons for the association between depression and dementia is unclear, though several potential mechanisms have been hypothesized, including depression as a contributory factor in vascular disease, inflammatory changes, changes in glucocorticoid steroids and hippocampal atrophy, increased deposition of B-amyloid plaques, and nerve growth factor deficits (summarized in [5]). Additionally, late-life depression may also be an early symptom of dementia [9]. Studies yield conflicting results regarding the temporality of the association, with some studies showing associations between dementia and early/midlife depression as well as late depression [6,8], while other studies showed associations

between dementia and early or midlife depression only [7]; still others revealed an association between dementia risk and late-life depression, but not early depression [9]. The discrepancies among these studies are likely due to variations in exposure and outcome measurements, varying statistical methodologies, and importantly, confounder control. However, the majority of studies do indicate a role for late-life depression in dementia and dementia pathology; indeed, a recent systematic review and meta-analysis concluded that late-life depression is consistently associated with a twofold increased risk of dementia [10].

At this time it is unknown whether pharmacological treatment for depression can alter the risk of developing dementia and AD. Treating depression may benefit those at risk of dementia by virtue of altering the pathobiological pathway between depression and dementia. Further potential rationale for antidepressants potentially contributing to a change in dementia risk status come from animal studies indicating that multiple classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), appear to have neurogenic and/or neuroprotective properties in animal models. Additionally, adding an SSRI to cholinesterase inhibitor treatment for AD provided greater benefit in activities of daily living (ADL) and cognition in individuals with cognitive impairment [11]. While concerns regarding the anticholinergic and sedative effects of TCAs remain [12], newer antidepressant classes (such as SSRIs) have been shown to either have no effect on, or a slight beneficial effect on, parameters measuring cognition in short randomized clinical trials and small observational studies in healthy adults (reviewed in [13]). However, few studies have directly addressed the association between antidepressant use and risk of dementia and AD.

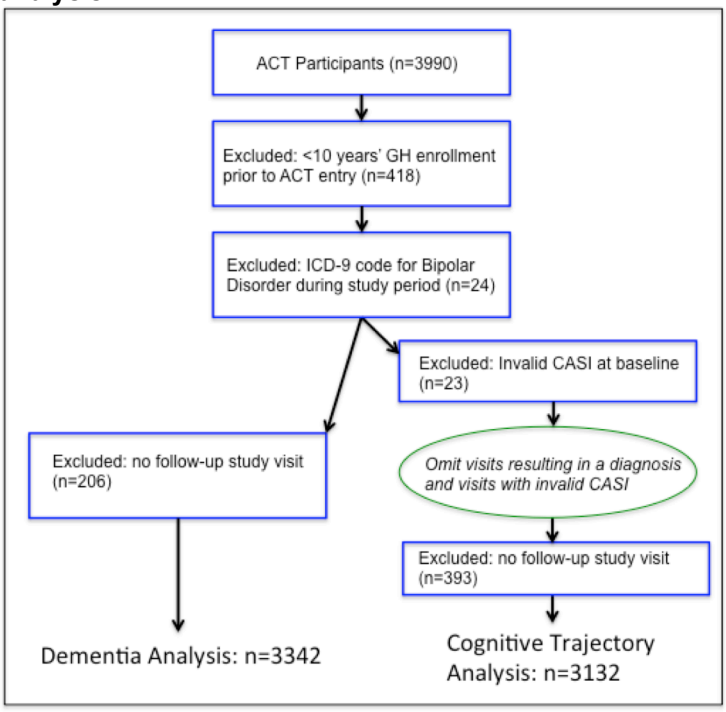
We used data from a population-based prospective cohort study with computerized pharmacy data going back 10 years prior to cohort entry to evaluate the association between cumulative antidepressant use and risk for dementia and cognitive decline. It was hypothesized that antidepressants with anticholinergic properties (TCAs and paroxetine) would be associated with higher risk of dementia and AD, while non-anticholinergic antidepressants (SSRIs, SARIs, and other) would be associated with a lowered risk of dementia and AD.

Methods

Design, study setting, and participants

The Adult Changes in Thought (ACT) study was undertaken to investigate, among other risk factors, the contributions to dementia risk of long-term use of a variety of commonly used medications. Study details have been described elsewhere [14]. Briefly, participants aged 65 and older were randomly sampled from Seattle area Group Health (GH) members, a nonprofit integrated delivery system that provides comprehensive health care on a pre-paid basis to approximately 620,000 individuals throughout Washington State and parts of Idaho. GH's administrative data files include demographics, enrollment, inpatient and outpatient diagnoses and procedures, breast services and results, pharmacy dispensings, laboratory results, vital signs, and death [15]. The pharmacy database includes all medications dispensed at GH's outpatient pharmacies as well as claims from contracting pharmacies. Pharmacy data are estimated to be 97% complete [15–17]. The initial cohort included 2581 participants enrolled from 1994-1996, with an additional 811 participants enrolled in 2000-2003. Continuous enrollment has occurred since 2004 to replace those who developed dementia, died, or dropped out. Participants were assessed at entry and returned biannually to evaluate cognitive function and collect demographic characteristics, medical history, health behaviors, and health status. Dementia screening was performed using the Cognitive Abilities Screening Instrument (CASI), which evaluates multiple categories of cognitive function [18]. Diagnosis of dementia and AD was made by consensus conference using standard criteria [19], as described previously [14]. All subjects enrolled (and not withdrawn due to reasons other than death) in the ACT study with at least one follow-up visit and 10 years of

Figure 1.1. Flowchart for participant inclusion in each analysis



prior membership in GH at enrollment were included for the analyses of dementia and AD risk (**Figure 1.1**). Additionally, ICD-9 codes from office visits and therapy visits were used to exclude individuals diagnosed with bipolar disorder (using ICD-9 codes 296.5 and 296.6). For the cognitive trajectory analysis, visits occurring after the estimated date of AD or dementia onset were not included; only subjects with a valid cognitive score at baseline were analyzed. Data through December 31, 2013, were included in these analyses.

Exposures

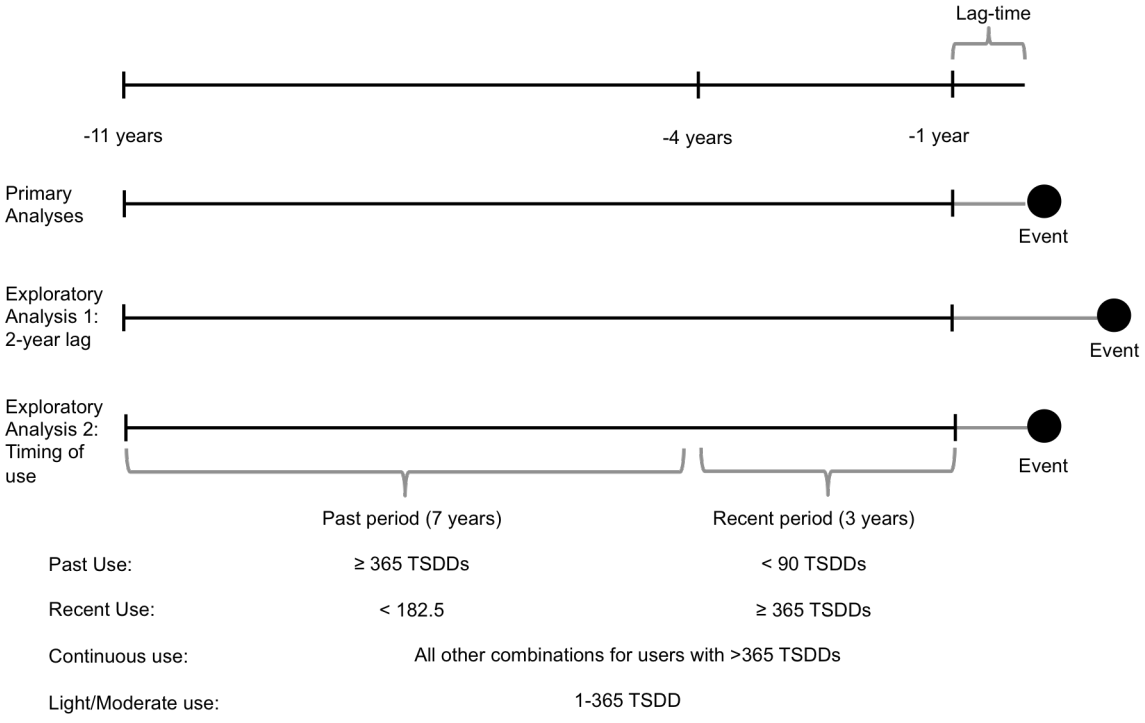
Prescription antidepressant use was identified from computerized pharmacy data, which included drug name, strength, route of administration, number of pills, and date dispensed. Subjects were defined as a user of a particular antidepressant medication class of interest if they had any dispensing of a medication in the class of interest during the study period (10 years prior to cohort entry through end of follow-up). For each dispensing, data collected in the GH pharmacy database included the generic name of the medication, number of tablets in the dispensing, and strength in milligrams of each tablet. SSRIs were the most common therapies for depression in the ACT cohort by the end of the study period, though TCAs were commonly prescribed earlier and within the time frame of the ACT cohort study, allowing us to examine all major classes of antidepressants. Among the SSRIs, paroxetine has high anticholinergic activity [20]. Thus, we grouped the other SSRI medications (fluoxetine, sertraline, citalopram, escitalopram, and fluvoxamine maleate) separately from paroxetine for analyses. Medication classes were grouped as follows: TCAs, other SSRIs, Paroxetine, SARIs, and Other (which included the less commonly used NDRIs, NaSSA, SNRIs, MAOIs, and TeCASs, details in **Table 1.3**).

To create the exposure measures, we calculated the total medication dose for each prescription fill by multiplying the tablet strength by the number of tablets dispensed. We then calculated a standard daily dose (SDD) by dividing the product by the minimum effective dose per day recommended for use in older adults [21]. For each participant, we summed the SDDs for each drug class at baseline and during each 10-year exposure period to creative a cumulative total SDD (TSDD, as done in [12]). To avoid protopathic bias, we excluded prescriptions in the most recent 1-year period before each event. Protopathic bias occurs when a medication is inadvertently prescribed for an early manifestation (e.g.,

depression) of a disease (e.g., dementia) that has not yet been diagnostically detected. The exposure varied over time, such that the 10-year TSDD was updated as the participants were followed up over their time in the study (i.e., at each event during follow-up, the ten-year TSDD was recalculated for all participants at risk). We categorized the TSDDs as no use, 1-90 TSDDs, 91-365 TSDDs, 366-1095 TSDDs, or >1095 TSDDs (i.e., >3 years). An exploratory analysis examined whether or not the timing of use influenced results in moderate users (≥ 365 TSDDs), with recent users defined as those with the majority of their use in the three years previous to the endpoint (≥365 TSDDs) and minimal use in the previous 7 years (<182.5 TSDDs); past users were defined as having minimal use in the immediate three years before the endpoint (<90 TSDDs), and the majority of their use in the previous seven years (≥365 TSDDs). A schematic of the time periods used for the primary and exploratory analyses is in **Figure 1.2**.

For the cognitive trajectory analysis, cumulative antidepressant exposure was defined by summing all the SDDs in the ten years previous to each visit during which the Cognitive Abilities Screening Instrument (CASI) [18] was administered. Visits leading to a dementia diagnosis were excluded, since CASI scores at these visits were often so low that they would have strongly influenced

Figure 1.2. Schema for exposure definition for dementia analyses. A rolling 10-year window was used to define the time-varying exposures. At each event during follow-up (minus one year lag-time), the 10-year cumulative exposure for all participants at risk was recalculated.



results and reflected the dementia analyses, rather than showing patterns of cognitive decline in healthy aging individuals. Thus there was no need to account for protopathic bias by excluding recent dispensings in this sample.

Outcomes

AD or dementia

Participants underwent cognitive screening at baseline and every two years using the CASI, which has a range of 0-100 (higher scores indicate better performance). A score <86 triggered standardized diagnostic evaluation for dementia, which included physical and neurological examination and neuropsychological testing. Results and clinical data were reviewed by a multidisciplinary consensus conference and assigned dementia and AD diagnoses [19]. The date of dementia onset was assigned as the midpoint between the study visit that triggered the dementia evaluation and the preceding visit. Participants diagnosed with dementia were re-evaluated after one year to confirm diagnosis.

Cognitive decline

The primary cognitive trajectory analysis used the CASI score at each biannual visit. An important challenge in using standard scoring of the CASI is that the distribution of item difficulties is not considered; for example, individuals with higher cognitive ability have few items with difficulty items close to their ability level, so their scores may appear more stable over time, while individuals with lower ability levels have more items whose difficulty level is close to their ability level, so their scores are more precise, and we can detect changes with greater sensitivity [22]. We therefore performed secondary analyses using item response theory (IRT) methods to generate CASI-IRT scores, which have linear scaling properties that take into account this problem of a ceiling effect of the CASI for high-functioning individuals.

Covariates

Covariate information was obtained from standardized questionnaires administered at each ACT study visit and GH electronic databases. Demographic factors included age, sex, race (white vs. non-

white), and education (some college education vs. no college education). Participants provided self-reported history of diabetes mellitus, hypertension, and coronary heart disease (which included ever reporting MI, angina, CABG, angioplasty, stroke, TIA, or CEA). Questionnaires ascertained self-reported health (poor or fair vs. good, very good, or excellent), smoking (ever, never, or current), and exercise (15 minutes at least three times per week). Body mass index was calculated as weight (kilograms) divided by height squared (meters), and categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (≥30 kg/m^2). For the dementia outcome analysis, a dichotomous indicator for baseline CASI score was included (≥92 vs. <92) in the models.

Depression was assigned using a combination of ACT data and GH office visit data. As depression is a condition that may resolve or go into remission over time (partially in response to antidepressant medications administered), it was modeled as time-varying, with status updated at each visit. ACT participants were administered the Center for Epidemiologic Studies Depression scale (CESD) at baseline and at each biannual visit [23]. The CESD is an effective screening tool for depressive symptoms; a score ≧ 10 was used as the threshold for an indicator for depression. However, this score does not capture depression that occurred before the study period or in between study visits that resolved before the next study visit, so ICD9-codes for major depressive disorder at GH office visits throughout the study period were also used as indicators for depression. The ICD-9 codes used were: 296.2x (major depressive disorder, single episode), 296.3x (major depressive disorder, recurrent episode), 311 (Depressive disorder, not elsewhere classified), and 300.4 (Dysthymic disorder).

Statistical analysis

We used multivariable Cox proportional hazards regression models with participants' age as the time scale to estimate hazard ratios and 95% confidence intervals for the association between antidepressant use and dementia or possible Alzheimer's disease [24]. All antidepressant classes (TCAs, paroxetine, other SSRIs, SARIs, and Other) were analyzed simultaneously in each model in order to account for overlapping use and/or drug switching. Participants were censored at the earlier of: their last ACT visit, disenrollment from the GH health care plan, or death if they did not have a dementia diagnosis; all data before December 31, 2013 was included. In addition, for the AD analysis, subjects diagnosed with

non-AD dementia were also censored at estimated onset of dementia. Separate models were fit for each outcome (all-cause dementia and possible AD). Antidepressant use and depression were modeled as time-varying measures. Values at study entry were used for all other covariates, which included age at study entry, sex, educational level, hypertension, diabetes, heart disease, smoking, BMI, CASI score, regular exercise, and self-reported health. We excluded observations with missing covariate information (n=).

In exploratory analyses, we extended the lag time to two years and excluded prescriptions during this period from the calculation of cumulative use, because prodromal depressive symptoms may occur earlier than one year before estimated onset. A second exploratory analysis examined whether or not the timing of use influenced results in moderate users (≥ 365 TSDDs), with time categories defined by the period of the majority of dispensings, as described above (**Figure 1.2**). Additionally, because depression is itself a risk factor for dementia and AD, we performed additional exploratory analyses in which we restricted the data set to participants who had ever been depressed, i.e. who had either received an ICD-9 code for depression as defined previously, or scored ≥10 on the CESD, in order to minimize confounding by indication.

For the cognitive trajectory analysis, we evaluated the average differences in rates of decline between user groups (with no use as the reference group for each antidepressant category) using linear regression models estimated via generalized estimating equations (GEE). GEE models account for repeated measures on individuals over time and provide a population-averaged approach, in order to investigate differences in population-averaged responses. We used a working independence correlation matrix and calculated standard errors using the Huber-White sandwich estimators (the 'robust' option in STATA), in order to take into account issues concerning heterogeneity and lack of normality [25]. We estimated the average difference in rate of cognitive decline, defined as change in CASI score per year, between user groups by including an interaction term between age at follow-up and level of cumulative exposure. Models were adjusted for the same covariates as the dementia/AD analyses. All analyses were performed with STATA SE 12 (StataCorp, College Station, TX, USA).

Results

In **Table 1.1**, we provide participant study characteristics, overall and by antidepressant use at study entry. If a participant had used any antidepressant in the 10 years up to study entry, they were included in the corresponding category. Since many participants took more than one prescription, class totals will not sum to the total N for the whole cohort. The mean age of the participants at study entry was 75 years; 91% were white, 59% were women, and 69% had some college education. 34% had at least one fill for an antidepressant in the 10 years before study entry; however, by the end of the study period,

Table 1.1. Baseline characteristics of participants[a] according to antidepressant use[b] at or before study entry

	All (n = 3342)	No Antidep (n = 2218)	Non-Parox SSRI (n = 315)	PAROX (n = 140)	TCA (n = 805)	SARI (n = 313)	Other (n = 103)
Age at entry, mean ± SD	75.0±6.3	75.1±6.3	74.4±6.6	74.2±6.7	75.7±6.6	75.1±6.6	72.5±5.1
Male, n (%)	1376 (41.2)	1042 (47.0)	94 (29.8)	43 (30.7)	222 (27.6)	79 (25.2)	47 (45.6)
Nonwhite, n (%)	294 (8.8)	200 (9.0)	18 (5.7)	12 (8.6)	67 (8.3)	30 (9.6)	4 (3.9)
College education (n=3341), mean ± SD	2316 (69.3)	1529 (69.0)	239 (75.9)	104 (74.3)	537 (66.7)	219 (70.0)	81 (78.6)
Obese (n=3262), n (%)	859 (26.3)	542 (24.9)	96 (31.7)	45 (34.6)	233 (30.0)	80 (26.4)	24 (24.7)
Depressed before or at entry[c], n (%)	710 (21.2)	181 (8.2)	269 (85.4)	123 (87.9)	322 (40.0)	186 (59.4)	70 (68.0)
Anxiety before or at entry, n (%)	295 (8.8)	92 (4.2)	116 (36.8)	55 (39.3)	119 (14.8)	78 (24.9)	36 (35.0)
CASI score at entry (n=3306), mean ± SD	93.7±4.6	93.8±4.7	93.6±4.7	93.8±4.7	93.3±4.7	93.6±4.9	94.5±4.8
Presence of APOE ε4 (n=2889), n (%)	762 (26.4)	508 (26.2)	66 (25.5)	31 (27.4)	179 (26.0)	69 (26.2)	27 (32.5)
Comorbid conditions at entry, n (%)							
Heart disease[d]	811 (24.3)	496 (22.4)	89 (28.3)	42 (30.0)	243 (30.2)	88 (28.1)	23 (22.3)
Diabetes mellitus (n=3333)	342 (10.3)	195 (8.8)	40 (12.7)	24 (17.1)	117 (14.6)	35 (11.2)	12 (11.8)
Hypertension (n=3312)	1369 (41.3)	859 (38.9)	154 (49.7)	76 (55.9)	353 (44.4)	144 (46.9)	50 (50.5)
Current smoking (n=3334), n (%)	155 (4.7)	90 (4.1)	15 (4.8)	3 (2.1)	50 (6.3)	15 (4.8)	9 (8.7)
History of smoking, n (%)	1526 (45.8)	1015 (45.8)	143 (45.5)	70 (50.0)	370 (46.1)	139 (44.7)	52 (50.5)
Fair or poor self-reported health (n=3333), n (%)	491 (14.7)	245 (11.1)	67 (21.3)	34 (24.3)	203 (25.3)	73 (23.5)	23 (22.6)
Regular exercise (n=3332), n (%)	2359 (70.8)	1611 (72.8)	214 (68.2)	85 (60.7)	528 (65.8)	206 (66.0)	60 (58.8)

[a]Only participants with two or more visits included, and must have enrolled in GHC at least 10 years before ACT entry. Individuals diagnosed with bipolar disorder excluded (n=24).
[b]All antidepressant prescriptions in the 10 years before ACT study entry were taken into account.
[c]Indicates a score of 10 or greater on the CESD, or an ICD9-code for depression at a previous office visit
[d]Heart Disease includes ever-reported MI, angina, CABG, angioplasty, stroke, TIA, or CEA
[e]Indicates at least 15 minutes of activity at least 3 times per week

almost half (48.6%) had used at least one antidepressant (**Table 1.2**). Participants who used antidepressants prior to study entry were, in general, more likely to be women, to have more diagnoses of depression and anxiety, to have fair or poor self-rated health, and to have comorbidities (hypertension, heart disease, and diabetes) than non-users. The most common antidepressant classes were TCAs and SSRIs, which together made up 80% of all cumulative doses (**Table 1.3**). The most common individual TCAs were doxepin, nortriptyline, and amitriptyline, while the most common SSRIs were fluoxetine, paroxetine, and sertraline.

Table 1.2. Characteristics and outcomes of participants[a] according to antidepressant use[b] during the study period

	All (n = 3342)	No Antidep (n = 1717)	Non-Parox SSRI (n = 652)	PAROX (n = 316)	Any TCA (n = 1110)	Any SARI (n = 600)	Any Other (n = 208)
Duration of follow-up, years, mean ± SD	7.9±5.1	7.6±5.1	8.4±5.1	8.3±4.5	8.3±5.0	8.9±5.1	8.0±5.1
Ever depressed, n (%)	1410 (42.2)	364 (21.2)	583 (89.4)	291 (92.1)	683 (61.5)	414 (69.0)	171 (82.2)
Ever anxiety, n (%)	678 (20.3)	153 (8.9)	303 (46.5)	158 (50.0)	342 (30.8)	250 (41.7)	102 (49.0)
Dementia dx	864 (25.9)	418 (24.3)	168 (25.8)	115 (36.4)	328 (29.6)	146 (24.3)	40 (19.2)
AD dx (possible AD)	699 (20.9)	339 (19.7)	130 (19.9)	89 (28.2)	260 (23.4)	120 (20.0)	25 (12.0)

[a]Only participants with two or more visits included, and must have enrolled in GHC at least 10 years before ACT entry. Individuals diagnosed with bipolar disorder excluded (n=24).
[b]Antidepressant prescriptions up to one year before event (censoring or dementia onset) included

During a mean follow-up of 7.9 years, 864 (25.9%) participants developed dementia, of which 699 (80.9%) were considered to have possible or probable AD. **Table 1.4** shows unadjusted and adjusted risk estimates for dementia and AD associated with antidepressant use, by class and dosage. Results for dementia and AD were similar: paroxetine use was associated with higher risk in a non-dose-dependent manner, with even the lowest exposure (1-90 TSDDs) showing significantly higher risk than non-users for dementia (adjusted HR, 1.68 [95% CI, 1.20-2.37]) and AD (adjusted HR, 1.72 [95% CI, 1.17-2.52]). Other SSRIs, however, were not associated with increased risk of dementia or AD at any exposure level compared to non-users. TCA use was associated with a slight non-significant increase in risk of dementia at the two higher exposure levels compared to non-users (for TSDD 366-1095, adjusted HR, 1.13 [95% CI, 0.81-1.56]; for TSDD >1095, adjusted HR, 1.16, [95% CI, 0.90-1.51]). Moderately high TCA users (TSDD, 366-1095) had a slight non-significant increased risk of AD (adjusted HR, 1.22 [95% CI, 0.85-1.74]).

Table 1.3. Total antidepressant prescription fills during study period

	Distinct individuals	Prescription fills		Cumulative SDDs	
Antidepressant	No.[b]	No.	%	No.	%
TCAs					
Nortriptyline	592	4725	11.9	786,716	12.7
Doxepin	382	4851	12.2	1,213,716	19.5
Amitriptyline	349	3703	9.3	862,406	13.9
Imipramine	221	1605	4.1	399,778	6.4
Desipramine	101	578	1.5	173,897	2.8
Perphenazine/Amitriptyline	3	207	0.5	2376	<0.1
Protriptyline	7	44	0.1	6181	0.1
Clomipramine HCL	3	5	<0.1	180	<0.1
SSRIs					
Fluoxetine	511	6820	17.2	701,080	11.3
Paroxetine	316	3242	8.2	302,749	4.9
Sertraline	179	2305	5.8	279,605	4.5
Citalopram	185	1813	4.6	233,370	3.8
Escitalopram	2	31	0.1	14,220	0.2
Fluvoxamine Maleate	2	12	<0.1	633	<0.1
SARI					
Trazodone	595	5508	13.9	904,072	14.6
Nefazodone	9	145	0.4	12,922	0.2
NDRIs					
Bupropion HCL	128	2558	6.5	157,257	2.5
NaSSA					
Mirtazapine	51	499	1.3	36,254	0.6
SNRI					
Venlafaxine	43	587	1.5	90,576	1.5
Duloxetine	3	34	0.1	4461	0.1
MAOI					
Selegiline	13	243	0.6	20,815	0.3
Phenelzine sulfate	2	8	<0.1	1262	<0.1
Tranylcypromine	1	13	<0.1	420	<0.1
TeCAs					
Maprotiline	4	119	0.3	8195	0.1

[a]Either time of any-cause dementia onset or the last dementia-free study visit before death or end of study.
[b]Subtotals within classes may not sum up to class totals due to patients who took multiple drugs within one class.

Table 1.4. Risk of dementia according to Antidepressant 10-year cumulative dosage[a,d], (n=3342)

	DEMENTIA			ALZHEIMER'S		
		Unadjusted[b]	Adjusted[c]		Unadjusted[b]	Adjusted[c]
TSDD[a]	No. of events	HR (95% CI)	HR (95% CI)	No. of events	HR (95% CI)	HR (95% CI)
SSRIs						
Other SSRI						
0	696	1	1	569	1	1
1-90	37	0.86 (0.61, 1.21)	0.81 (0.56, 1.16)	32	0.90 (0.62, 1.30)	0.82 (0.55, 1.21)
91-365	47	1.24 (0.90, 1.71)	1.01 (0.72, 1.42)	29	0.94 (0.63, 1.41)	0.74 (0.48, 1.14)
366-1095	23	1.02 (0.66, 1.56)	0.88 (0.56, 1.40)	20	1.19 (0.76, 1.87)	1.03 (0.64, 1.66)
1095+	61	1.30 (0.97, 1.74)	1.07 (0.78, 1.47)	49	1.32 (0.95, 1.83)	1.06 (0.74, 1.51)
Paroxetine						
0	749	1	1	610	1	1
1-90	43	1.61 (1.16, 2.25)	1.68 (1.20, 2.37)	34	1.64 (1.13, 2.39)	1.72 (1.17, 2.52)
91-365	28	1.45 (0.97, 2.18)	1.46 (0.95, 2.24)	21	1.41 (0.88, 2.26)	1.51 (0.92, 2.47)
366-1095	22	2.07 (1.32, 3.24)	2.06 (1.30, 3.28)	16	1.98 (1.17, 3.35)	1.92 (1.11, 3.33)
1095+	22	1.95 (1.24, 3.08)	1.49 (0.89, 2.49)	18	1.98 (1.19, 3.29)	1.66 (0.95, 2.88)
TCA						
0	536	1	1	439	1	1
1-90	87	1.03 (0.81, 1.32)	0.93 (0.72, 1.20)	75	1.08 (0.83, 1.41)	0.97 (0.73, 1.28)
91-365	91	1.15 (0.89, 1.48)	1.09 (0.84, 1.41)	68	0.99 (0.73, 1.33)	0.95 (0.70, 1.30)
366-1095	53	1.29 (0.95, 1.76)	1.13 (0.81, 1.56)	42	1.33 (0.95, 1.87)	1.22 (0.85, 1.74)
1095+	97	1.32 (1.03, 1.69)	1.16 (0.90, 1.51)	75	1.18 (0.89, 1.57)	1.07 (0.79, 1.44)
SARI						
0	718	1	1	579	1	1
1-90	50	0.64 (0.46, 0.88)	0.64 (0.46, 0.89)	45	0.75 (0.54, 1.05)	0.74 (0.52, 1.04)
91-365	44	0.98 (0.70, 1.36)	0.92 (0.66, 1.30)	34	0.94 (0.64, 1.37)	0.91 (0.62, 1.33)
366-1095	24	0.95 (0.59, 1.51)	0.86 (0.53, 1.41)	15	0.77 (0.43, 1.38)	0.77 (0.43, 1.38)
1095+	28	0.94 (0.62, 1.42)	0.80 (0.52, 1.24)	26	1.14 (0.74, 1.76)	0.96 (0.61, 1.52)
Other						
0	824	1		674	1	1
1-90	7	0.41 (0.18, 0.93)	0.30 (0.12, 0.73)	5	0.35 (0.13, 0.95)	0.23 (0.07, 0.71)
91-365	12	1.76 (0.95, 3.25)	1.50 (0.78, 2.86)	6	1.17 (0.51, 2.67)	0.89 (0.36, 2.19)
366-1095	9	1.50 (0.73, 3.07)	1.05 (0.46, 2.41)	6	1.16 (0.47, 2.84)	0.89 (0.33, 2.45)
1095+	12	1.47 (0.82, 2.64)	1.45 (0.80, 2.65)	8	1.22 (0.59, 2.50)	1.16 (0.56, 2.41)

[a]Total Standardized Daily Dose by sliding window 10-year cumulative standard daily dosages. Prescriptions up to one year before last visit or onset for those with dementia diagnosis included.
[b]Adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously) and age (via the time-axis)
[c]Adjusted further for cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week).
[d]Individuals with bipolar disorder excluded

Risk estimates did not appreciably change (**Table 1.5**) when we extended the lag time to two years in secondary analyses. Similarly, when we analyzed participants who had ever had depression (**Table 1.6**) at any time during the study period, some risk estimates appeared slightly elevated, though the sample size was small (N=1410) and confidence intervals were quite large.

The exploratory analysis investigating the timing of the majority of prescriptions among the moderate-to-heavy users (>365 TSDDs in a 10-year window) revealed that for paroxetine users, past use and light-to-moderate use were associated with significant increased risk of dementia (**Table 1.7**) (light/moderate use HR: 1.66, 95% CI, 1.25, 2.20; past use HR: 2.13, 95% CI, 1.20, 3.79). Recent and continuous use was also associated with increased risk of dementia, though confidence intervals crossed

Table 1.5. Risk of dementia and Alzheimer's disease according to antidepressant 10-year cumulative dosage[a,d] with two year lag time, (n=3342)

	DEMENTIA		ALZHEIMER'S	
	Unadjusted[b]	Adjusted[b]	Unadjusted[b]	Adjusted[c]
TSDD[a]	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
SSRIs				
Other SSRI				
0	1	1	1	1
1-90	0.91 (0.65, 1.28)	0.94 (0.66, 1.33)	0.93 (0.64, 1.34)	0.95 (0.65, 1.40)
91-365	0.94 (0.65, 1.35)	0.78 (0.53, 1.16)	0.82 (0.53, 1.26)	0.67 (0.42, 1.07)
366-1095	1.16 (0.79, 1.71)	1.12 (0.74, 1.68)	1.19 (0.77, 1.83)	1.13 (0.72, 1.78)
1095+	1.01 (0.72, 1.40)	0.86 (0.60, 1.23)	1.03 (0.71, 1.50)	0.87 (0.58, 1.30)
Paroxetine				
0	1	1	1	1
1-90	1.61 (1.15, 2.26)	1.67 (1.18, 2.36)	1.56 (1.06, 2.30)	1.59 (1.07, 2.37)
91-365	1.45 (0.96, 2.20)	1.55 (1.00, 2.39)	1.42 (0.89, 2.28)	1.59 (0.98, 2.60)
366-1095	1.67 (0.99, 2.81)	1.67 (0.97, 2.89)	1.62 (0.88, 2.97)	1.58 (0.83, 3.00)
1095+	2.15 (1.38, 3.35)	1.71 (1.03, 2.82)	2.19 (1.34, 3.59)	1.91 (1.12, 3.27)
TCA				
0	1	1	1	1
1-90	1.14 (0.90, 1.44)	1.01 (0.79, 1.29)	1.16 (0.89, 1.50)	1.01 (0.77, 1.33)
91-365	1.09 (0.84, 1.42)	1.06 (0.80, 1.38)	0.98 (0.73, 1.33)	0.98 (0.71, 1.34)
366-1095	1.39 (1.02, 1.88)	1.25 (0.91, 1.72)	1.44 (1.04, 2.01)	1.38 (0.98, 1.94)
1095+	1.35 (1.06, 1.72)	1.19 (0.92, 1.55)	1.23 (0.93, 1.63)	1.12 (0.83, 1.51)
SARI				
0	1	1	1	1
1-90	0.72 (0.53, 0.98)	0.72 (0.52, 0.99)	0.78 (0.56, 1.09)	0.76 (0.54, 1.08)
91-365	1.03 (0.75, 1.43)	0.97 (0.70, 1.36)	1.03 (0.72, 1.49)	1.00 (0.69, 1.45)
366-1095	0.93 (0.58, 1.51)	0.79 (0.48, 1.33)	0.72 (0.39, 1.33)	0.66 (0.35, 1.24)
1095+	0.94 (0.60, 1.45)	0.83 (0.53, 1.31)	1.18 (0.75, 1.85)	1.02 (0.64, 1.63)
Other				
0	1		1	1
1-90	0.63 (0.31, 1.27)	0.55 (0.27, 1.11)	0.30 (0.10, 0.93)	0.25 (0.08, 0.79)
91-365	1.38 (0.67, 2.83)	1.09 (0.51, 2.37)	1.02 (0.41, 2.52)	0.73 (0.28, 2.02)
366-1095	1.99 (1.01, 3.91)	1.53 (0.71, 3.30)	1.62 (0.71, 3.70)	1.39 (0.56, 3.43)
1095+	1.36 (0.69, 2.66)	1.40 (0.70, 2.79)	1.14 (0.50, 2.59)	1.10 (0.47, 2.55)

[a]Total Standardized Daily Dose by sliding window 10-year cumulative standard daily dosages. Prescriptions up to one year before last visit or onset for those with dementia diagnosis included.
[b]Adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously) and age (via the time-axis)
[c]Adjusted further for cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week).
[d]Individuals with bipolar disorder excluded

1. Conversely, among non-paroxetine users and TCA users, recent and continuous use was associated with highest risk of dementia, while light/moderate and past use was not associated with dementia risk, though results were not significant. Results were similar for AD.

The average CASI score at baseline for the entire cohort was 93.7, with similar scores seen for all classes of antidepressant users (93.3-94.5). **Table 1.8** shows the mean difference (in CASI points per year) between users and non-users in the first results column, while the second column shows the actual mean point change in CASI per year for each exposure level. For instance, when we compare SSRI

Table 1.6. Risk of dementia and Alzheimer's disease according to antidepressant 10-year cumulative dosage[a,d] in individuals with depression, (n=1410)

	DEMENTIA		ALZHEIMER'S	
	Unadjusted[b]	Adjusted[b]	Unadjusted[b]	Adjusted[c]
TSDD[a]	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
SSRIs				
Other SSRI				
0	1	1	1	1
1-90	0.78 (0.52, 1.16)	0.73 (0.48, 1.12)	0.79 (0.51, 1.22)	0.73 (0.45, 1.17)
91-365	1.27 (0.90, 1.79)	1.04 (0.73, 1.50)	0.89 (0.58, 1.39)	0.72 (0.45, 1.16)
366-1095	0.99 (0.63, 1.56)	0.89 (0.55, 1.45)	1.13 (0.70, 1.84)	1.05 (0.64, 1.74)
1095+	1.32 (0.96, 1.81)	1.03 (0.73, 1.44)	1.36 (0.96, 1.93)	1.06 (0.73, 1.53)
Paroxetine				
0	1	1	1	1
1-90	1.79 (1.25, 2.57)	1.94 (1.34, 2.81)	1.76 (1.16, 2.66)	1.91 (1.25, 2.93)
91-365	1.54 (1.02, 2.34)	1.52 (0.98, 2.37)	1.43 (0.88, 2.31)	1.54 (0.93, 2.55)
366-1095	2.26 (1.42, 3.59)	2.31 (1.44, 3.71)	2.01 (1.16, 3.49)	2.14 (1.22, 3.73)
1095+	2.04 (1.27, 3.28)	1.60 (0.93, 2.74)	2.14 (1.28, 3.59)	1.86 (1.06, 3.28)
TCA				
0	1	1	1	1
1-90	0.90 (0.65, 1.25)	0.85 (0.60, 1.19)	0.98 (0.69, 1.39)	0.93 (0.65, 1.34)
91-365	1.01 (0.72, 1.41)	1.02 (0.72, 1.44)	0.92 (0.62, 1.35)	0.94 (0.63, 1.40)
366-1095	1.14 (0.77, 1.69)	1.08 (0.72, 1.63)	1.14 (0.74, 1.76)	1.10 (0.70, 1.75)
1095+	1.30 (0.97, 1.73)	1.23 (0.90, 1.67)	1.22 (0.87, 1.70)	1.21 (0.86, 1.72)
SARI				
0	1		1	1
1-90	0.63 (0.42, 0.94)	0.66 (0.44, 1.00)	0.74 (0.49, 1.14)	0.78 (0.50, 1.20)
91-365	1.06 (0.73, 1.54)	0.99 (0.67, 1.46)	1.02 (0.66, 1.56)	0.98 (0.63, 1.51)
366-1095	1.03 (0.61, 1.72)	1.00 (0.59, 1.70)	0.81 (0.42, 1.54)	0.83 (0.43, 1.59)
1095+	0.95 (0.59, 1.51)	0.87 (0.53, 1.43)	1.20 (0.74, 1.94)	1.15 (0.69, 1.93)
Other				
0	1		1	1
1-90	0.25 (0.08, 0.79)	0.22 (0.07, 0.69)	0.22 (0.05, 0.88)	0.18 (0.05, 0.75)
91-365	1.84 (0.96, 3.54)	1.61 (0.81, 3.22)	1.10 (0.44, 2.75)	0.84 (0.30, 2.32)
366-1095	1.30 (0.60, 2.80)	1.09 (0.47, 2.53)	1.12 (0.45, 2.77)	0.84 (0.30, 2.35)
1095+	1.33 (0.70, 2.56)	1.21 (0.62, 2.37)	1.16 (0.54, 2.53)	0.99 (0.45, 2.21)

[a]Total Standardized Daily Dose by sliding window 10-year cumulative standard daily dosages. Prescriptions up to one year before last visit or onset for those with dementia diagnosis included.
[b]Adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously) and age (via the time-axis)
[c]Adjusted further for cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week).
[d]Individuals with bipolar disorder excluded

users to non-users, the average rate of decline in non-users was 0.11 points per year. SSRI users in the highest exposure category (+1095) declined 0.05 points per year faster than non-users (95% CI, -0.10, -0.004, interaction p-value=0.032), resulting in an average rate of decline of 0.16 points per year in the heaviest SSRI users. In general, aside from this indication that heavy SSRI users are declining at a slightly faster rate than non-users, medication use did not affect mean rates of cognitive decline compared to non-users. Patterns were similar when using the CASI-IRT scores to take into account ceiling effects (**Table 1.9**).

Table 1.7. Risk of dementia and Alzheimer's disease according to timing of use for individuals with total cumulative SDDs > 365

	Dementia[b,c]		Alzheimer's[b,c]	
Characteristic	# events	HR (95% CI)	# events	HR (95% CI)
SSRI Use[a]				
Other SSRI				
0	703	1	574	**1**
Light/Moderate	82	0.91 (0.70, 1.18)	58	0.78 (0.57, 1.06)
Past	8	0.67 (0.33, 1.37)	6	0.63 (0.27, 1.43)
Recent	30	1.16 (0.77, 1.74)	26	1.24 (0.81, 1.92)
Continuous	44	1.06 (0.73, 1.53)	35	1.04 (0.69, 1.57)
Parox Use[a]				
0	757	1	616	**1**
Light/Moderate	69	1.66 (1.25, 2.20)	52	1.68 (1.21, 2.31)
Past	15	2.13 (1.20, 3.79)	12	2.34 (1.25, 3.40)
Recent	9	1.71 (0.85, 3.35)	6	1.50 (0.66, 4.38)
Continuous	17	1.58 (0.91, 2.72)	13	1.52 (0.82, 2.82)
TCA Use[a]				
0	595	1	490	1
Light/Moderate	146	1.01 (0.83, 1.22)	112	0.96 (0.77, 1.20)
Past	43	0.95 (0.68, 1.32)	37	0.99 (0.69, 1.42)
Recent	20	1.65 (1.02, 2.66)	14	1.44 (0.81, 2.57)
Continuous	63	1.22 (0.92, 1.63)	46	1.21 (0.88, 1.68)
SARI Use[a]				
0	741	1	596	1
Light/Moderate	81	0.74 (0.58, 0.95)	68	0.80 (0.61, 1.05)
Past	12	0.83 (0.45, 1.53)	9	0.84 (0.43, 1.65)
Recent	15	1.01 (0.57, 1.76)	10	0.91 (0.46, 1.77)
Continuous	18	0.72 (0.43, 1.21)	16	0.88 (0.51, 1.51)
OTHER Use[a]				
0	828	1	676	1
Light/Moderate	19	0.67 (0.39, 1.13)	10	0.42 (0.20, 0.85)
Past	2	0.89 (0.13, 6.45)	0	NA
Recent	9	1.31 (0.64, 2.68)	6	1.00 (0.41, 2.47)
Continuous	9	1.48 (0.74, 2.94)	7	1.30 (0.60, 2.83)

[a]Dosage: Light/Moderate (<365 TSDDs in any time period); past (<90 SDDs within 3 years of endpoint, >=365 in previous 7 years); recent (>=365 SDDs within 3 years of endpoint, <182.5 in previous 7 years); continuous (all other combinations)
[b]Adjusted for all other medication use (all three medications analyzed in same model), age (via time axis, cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week).
[c]Individuals with bipolar disorder excluded

Discussion

In this population-based longitudinal study of older adults, we observed an association between paroxetine use and increased risk of dementia, even among the lightest users (1-90 TSDDs) and past users. We did not find associations between other SSRI use, or TCA use, and risk of dementia. Non-paroxetine SSRI use was associated with a slightly increased rate of cognitive decline among the heaviest users only, and we did not observe associations between other classes of antidepressants and rate of cognitive decline. The dementia and AD risk results were robust in secondary analyses, which increased the lag time during which prescriptions were excluded from one to two years to account for prodromal symptoms of dementia, and in analyses examining dementia risk and antidepressant use in the subset of the cohort that had experienced depression at any time.

Table 1.8. Mean CASI score difference[a] per year between users and non-users, and total rate of change (in CASI score) by levels of cumulative antidepressant use[c]

TSDD	Mean difference in change in CASI score per year (95% CI)[b]	Mean change in CASI score per year (95% CI)	Interaction p-value
SSRI			
Other SSRI			
Untreated	Reference	-0.11 (-0.12, -0.10)	NA
1-90	-0.04 (-0.1, 0.01)	-0.15 (-0.21, -0.10)	0.137
91-365	-0.02 (-0.09, 0.05)	-0.13 (-0.20, -0.06)	0.515
366-1095	-0.03 (-0.09, 0.04)	-0.14 (-0.20, -0.07)	0.419
1095+	-0.05 (-0.10, -0.004)	-0.16 (-0.20, -0.12)	0.032
Paroxetine			
Untreated	Reference	-0.11 (-0.13, -0.10)	NA
1-90	-0.02 (-0.08, 0.03)	-0.14 (-0.19, -0.08)	0.432
91-365	0.00 (-0.07, 0.07)	-0.11 (-0.18, -0.04)	0.938
366-1095	-0.06 (-0.20, 0.07)	-0.18 (-0.31, -0.04)	0.353
1095+	0.08 (-0.06, 0.22)	-0.04 (-0.18, 0.11)	0.278
TCA			
Untreated	Reference	-0.11 (-0.13, -0.10)	NA
1-90	-0.03 (-0.06, 0.01)	-0.14 (-0.17, -0.11)	0.114
91-365	0.01 (-0.04, 0.06)	-0.10 (-0.15, -0.06)	0.676
366-1095	-0.04 (-0.08, 0.01)	-0.15 (-0.20, -0.10)	0.149
1095+	0.01 (-0.04, 0.05)	-0.10 (-0.15, -0.06)	0.733
SARI			
Untreated	Reference	-0.12 (-0.13, -0.10)	NA
1-90	0.00 (-0.05, 0.06)	-0.11 (-0.16, -0.06)	0.868
91-365	-0.03 (-0.09, 0.04)	-0.14 (-0.21, -0.07)	0.468
366-1095	0.06 (-0.01, 0.14)	-0.05 (-0.13, 0.02)	0.103
1095+	0.02 (-0.07, 0.10)	-0.10 (-0.18, -0.01)	0.685
OTHER			
Untreated	Reference	-0.11 (-0.12, -0.10)	NA
1-90	-0.06 (-0.13, 0.02)	-0.17 (-0.24, -0.09)	0.141
91-365	-0.17 (-0.34, -0.01)	-0.29 (-0.45, -0.12)	0.036
366-1095	-0.03 (-0.14, 0.08)	-0.14 (-0.25, -0.04)	0.573
1095+	-0.06 (-0.15, 0.04)	-0.17 (-0.26, -0.08)	0.238

[a]Linear regression with generalized estimating equations to account for repeated observations per participant
[b]Models adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously), cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week).
[d]Individuals with bipolar disorder excluded

A comparative–effectiveness review found that second-generation antidepressants (which included all of the SSRIs in our study) do not substantially differ from each other in terms of efficacy [31], so untreated depression by one medication would not appear to be the cause in the differential risk findings between paroxetine and other SSRIs. Paroxetine does have higher affinity for muscarinic acetylcholine receptors compared with other SSRIs [32], though the affinity was lower compared with amitriptyline and desipramine, two common TCAs in our study. If anticholinergic properties alone were the reason for the observed association between paroxetine and increased risk of dementia, we should see similar risk profiles among the TCA users. However, TCA use was not associated with increased risk

Table 1.9. Mean CASI-IRT score difference[a] per year between users and non-users, and total rate of change (in CASI-IRT score) by levels of cumulative antidepressant use[c]

TSDD	Mean difference in change in CASI-IRT score per year (95% CI)[b]	Mean change in CASI-IRT score per year (95% CI)	Interaction p-value
SSRI			
Other SSRI			
Untreated	Reference	-0.0203 (-0.0224, -0.0182)	NA
1-90	-0.0124 (-0.0223, -0.0026)	-0.0327 (-0.0425, -0.0229)	0.013
91-365	-0.0017 (-0.0112, 0.0077)	-0.0220 (-0.0314, -0.0127)	0.719
366-1095	0.0016 (-0.0079, 0.0111)	-0.0187 (-0.0281, -0.0093)	0.741
1095+	-0.0075 (-0.0149, -0.0002)	-0.0278 (-0.0349, -0.0207)	0.045
Paroxetine			
Untreated	Reference	-0.0208 (-0.0229, -0.0188)	NA
1-90	-0.0069 (-0.0174, 0.0036)	-0.0277 (-0.0381, -0.0173)	0.200
91-365	-0.0029 (-0.0153, 0.0094)	-0.0238 (-0.0360, -0.0115)	0.642
366-1095	-0.0032 (-0.0202, 0.0139)	-0.0240 (-0.0409, -0.0071)	0.714
1095+	0.0072 (-0.0092, 0.0235)	-0.0137 (-0.0299, 0.026)	0.390
TCA			
Untreated	Reference	-0.0208 (-0.0231, -0.0186)	NA
1-90	-0.0025 (-0.0089, 0.0039)	-0.0233 (-0.0294, -0.0172)	0.440
91-365	0.0029 (-0.0049, 0.0108)	-0.0179 (-0.0255, -0.0103)	0.465
366-1095	-0.0068 (-0.0139, 0.0003)	-0.0276 (-0.0344, -0.0208)	0.061
1095+	0.0016 (-0.0054, 0.0086)	-0.0192 (-0.0259, -0.0125)	0.657
SARI			
Untreated	Reference	-0.0210 (-0.0231, -0.0189)	NA
1-90	-0.0012 (-0.0090, 0.0066)	-0.0222 (-0.0298, -0.0157)	0.767
91-365	-0.0013 (-0.0118, 0.0091)	-0.0224 (-0.0327, -0.0120)	0.802
366-1095	0.0051 (-0.0096, 0.0198)	-0.0159 (-0.0305, -0.0014)	0.499
1095+	0.0026 (-0.0086, 0.0137)	-0.0184 (-0.0294, -0.0075)	0.648
OTHER			
Untreated	Reference	-0.0206 (-0.0226, -0.0186)	NA
1-90	-0.0056 (-0.0168, 0.0055)	-0.0262 (-0.0373, -0.0152)	0.323
91-365	-0.0176 (-0.0345, -0.0007)	-0.0382 (-0.0551, -0.0214)	0.041
366-1095	-0.0184 (-0.0338, -0.0029)	-0.0390 (-0.0544, -0.0236)	0.020
1095+	-0.0075 (-0.0248, 0.0097)	-0.0282 (-0.0453, -0.01107)	0.390

[a]Linear regression with generalized estimating equations to account for repeated observations per participant
[b]Models adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously), cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week).
[d]Individuals with bipolar disorder excluded

of dementia and AD, although it trended in that direction. Paroxetine was commonly prescribed in the ACT cohort for a limited time in the late 90s, but has since fallen out of favor due to emergence of other antidepressant medications with fewer side effects along with changes in Group Health general practice, though it is still commonly used for the treatment of depression among elderly patients [33]. Confounding by indication cannot be ruled out in our study, as individuals with more severe depression or anxiety may have been more likely to try paroxetine, though the results seen here are plausible, given the known risk due to other highly anticholinergic medications [12]. At this time we are not able to explain the high risk seen in light users at any time and in past users; future studies may be able to untangle this by including

more detailed information regarding the specific clinical indication(s) attached to any given antidepressant medication.

To date, few studies have addressed antidepressant use and risk of dementia and AD directly [12,26–29]. Our study findings are not consistent with these few published reports, though none separated paroxetine from other SSRIs in their analyses. Two studies employed the Danish pharmacy register [26,27], which encompasses the entire population of Denmark. The first study examined all purchasers of antidepressants by class: SSRIs, newer non-SSRIs, and older antidepressants (specific medications in each class were not given). [27] The authors observed the risk of dementia and AD slightly declined among heaviest users of SSRIs and newer non-SSRIs compared to light and moderate users, though the risk never decreased among the heavy users to the level seen in non-users and individuals with only one or two prescriptions. The second Danish study [26] examined individuals with more severe depression (those who had been hospitalized), and found that individuals who used older antidepressants (most likely TCAs) experienced a slight decrease in dementia risk, though this was not seen in users of other medications. However, in these studies, the timing of the medication use was not taken into account. All purchases of prescriptions were counted, and it is possible that some individuals purchased antidepressants for prodromal symptoms of antidepressants, which would bias the results. In a retrospective cohort study, Wang et al. also observed an increased risk of dementia in multiple classes of antidepressants, with the highest risk seen in individuals who had only used SSRIs [29]. Individuals who used non-SSRIs (unspecified) also had increased risk of dementia, though individuals with mixed use (non-SSRI and SSRI) did not have increased risk of dementia, even though they had many more prescription fills and time on medication. The study authors concluded that patients in the mixed group were more likely to be resistant to antidepressant treatment, and perhaps also immune to other harmful effects of antidepressants on the brain. While this study had relatively rigorous classification of depression and longer follow-up times than other studies (up to 18 years), there was no accounting for prescriptions that were indicated for prodromal symptoms of depression.

Anticholinergic medications are not recommended in elderly populations due to risk of impaired cognitive and physical outcomes, as well as risk of dementia [30,31]. A recent study confirmed that the use of anticholinergic medications was associated with increased brain atrophy and dysfunction and

clinical decline [20]. An important previous study examined associations between anticholinergic medication use and dementia in the ACT cohort [12]. Utilizing similar methods to this study, the authors observed an increased risk of dementia and AD among the heaviest users of anticholinergic medications. A supplementary analysis showed a similar effect when the analysis was restricted to anticholinergic antidepressants; this analysis combined TCAs, paroxetine, and amoxapine. We did not find a statistically significant association between TCAs alone and dementia risk, though the HRs increased in a non-significant dose-dependent fashion, consistent with the previous ACT study result. Considering the results of the current study showing increasing dementia risk associated with paroxetine use, it is possible that paroxetine users primarily drove the increased risk shown in the anticholinergic supplementary analysis in the prior study, though the primary analysis in that study confirmed the risk of dementia associated with overall anticholinergic burden. However, the ACT study results conflict with a recent case-control study, which found a decreased risk of dementia specifically in TCA users at all cumulative dosages, especially the heaviest users (adjusted OR for cumulative dose >10,500 mg: 0.13, 95% CI, 0.11, 0.15), while SSRIs and other antidepressants were associated with increased risk of dementia (adjusted OR for cumulative dose >10,500 mg: 3.07, 95% CI, 2.69, 3.51) [28]. The potential for reverse causation cannot be ruled out in this study; it is possible that prescribers either consciously or unconsciously were more likely to prescribe SSRIs rather than TCAs to older patients with cognitive impairment or other health conditions, in order to avoid adverse effects attributable to anticholinergic medications. If this was the case, individuals at higher risk for dementia were simply more likely to be prescribed SSRIs, which would create a bias in favor of TCAs.

As mentioned, the previous studies grouped all SSRIs together. We found one additional study examining dementia risk in elderly nursing home patients which noted the anticholinergic properties of paroxetine, and examined risk of dementia among users of paroxetine and other SSRIs separately [32]; this was strictly a comparison analysis between patients on SSRIs and those on paroxetine, so overall associations between medication use or non-use on dementia risk was not assessed. Though they did not observe any difference between paroxetine and other SSRIs on associations with dementia risk, the follow-up time was relatively short (maximum of two years after first prescription), no lag time for

prodromal symptoms of dementia was incorporated, and the population was restricted to nursing home patients.

Antidepressant use may also impact rates of cognitive decline, though research has been limited by small sample sizes (n<100), short follow-up (<1 year), and lack of comparison groups [33]. Several studies have examined the hypothesis that antidepressant use may slow cognitive decline among patients who were already experiencing cognitive impairment and/or patients in early stages of dementia. Adding fluoxetine to a cholinesterase inhibitor provided greater benefits in activities of daily living and cognition in individuals with AD [11], while another study found little cognitive improvement in response to sertraline treatment in patients with cognitive impairment [34]. These studies also suffered from small sample sizes and short follow-up times. Recently, a few studies have begun to more comprehensively examine whether antidepressant treatment affects cognitive outcomes in cognitively healthy aging people with larger population sizes and longer follow-up times. The Women's Health Initiative Memory Study examined antidepressant use, depression, and progression to mild cognitive impairment in a large cohort of postmenopausal women [35], and found that SSRIs and TCAs, as well as depression (treated and untreated) were all associated with increased risk of mild cognitive impairment, though statistical power was limited due to small numbers of events after stratification by depression/medication status. Alternatively, our study results were more consistent with results obtained from the Health and Retirement Study [33], which did not observe a different rate of cognitive decline in antidepressant users compared to non-users over a 6-year period, though all classes of antidepressants were combined into one category. Our results showed that in general, antidepressant use did not impact rates of cognitive decline compared to non-users, with the exception of a potential increased rate of cognitive decline among heavy users of non-paroxetine SSRIs. However, it was not a strong affect, nor were our analyses corrected for multiple comparisons, so we cannot rule out a false positive. Though we originally hypothesized that heavy non-paroxetine SSRI use may be beneficial (both in terms of dementia risk and cognitive decline) due to disruption of the adverse effects of depression and neurogenic activity of SSRIs, individuals who heavily use SSRIs may have more resistant depression or other health conditions that would increase their risk for poor cognitive outcomes.

Our study had several limitations. Some medications classed as antidepressants were prescribed for symptoms not attributable to depression, such as insomnia and anxiety. Additionally, people who fill a prescription but do not ingest the medication and who obtain medications at non-GH pharmacies with no claim submitted to GH may be misclassified, but GH enrollees obtain almost all of their prescription medications at GH pharmacies or contracting pharmacies [15–17] and any misclassification is likely non-differential. Another limitation is the potential misclassification of confounders, particularly depression. Patients prescribed an antidepressant are much more likely to receive an ICD-9 code for depression than subjects not started on antidepressants. Thus, we may have failed to detect individuals with depression who were not treated, or who were treated with psychotherapy. All the analyses, particularly the exploratory analyses concerning timing of medication use, required stratifying the data such that some strata had relatively few cases, which decreased statistical power to detect true effects. When considering the negative results of the cognitive trajectory analysis, it should be noted that the CASI is likely to have high ceiling effects, as many participants in the ACT cohort were achieving maximum or near maximum scores at baseline and throughout the study period. Furthermore, the CASI is a screening tool, and as such may not be sensitive enough to detect differences over time, especially in those individuals performing at high cognitive functioning. Lastly, since the ACT cohort is a relatively homogeneous group of people in a relatively small geographical area, generalizability may be limited.

Our study had several strengths as well. It is the first study to assess the effect of use of multiple classes of antidepressants, by detailed dosage that varied over time, on AD risk and cognitive decline in an aging cohort, and is the first to examine the effects of paroxetine separately from other SSRIs. The ACT study is one of the largest and most detailed of its kind. Computerized pharmacy records enabled us to fully characterize dosage and duration of medications in greater detail than comparable studies; additionally, participants in the cohort were enrolled and followed for longer than most studies evaluating AD risk and cognition over time (8-9 years on average). Pertinent health data was recorded at each biannual visit, allowing us to include multiple covariates in our study that are often overlooked, although some residual confounding may still occur. Careful biannual cognitive screening allows for timely diagnosis capture and the ability to track trends in cognition over time. Additionally, timely diagnoses of

AD and dementia allow us to take into account symptoms and medications prescribed due to prodromal symptoms.

Our results suggest an increased risk of dementia in persons taking paroxetine, even for short lengths of time, while other antidepressants did not impact risk of dementia. Given the wide availability of safe, effective antidepressant medications that do not have anticholinergic properties, prescribers should be aware of the potential risks of these medications compared to others for older adults. Additional studies that include more detailed information regarding indications for medications dispensed are needed to untangle potential confounding influences on these findings.

Chapter 2

Apolipoprotein E ε4 as an effect modifier: depression, antidepressants, and risk of dementia and Alzheimer's disease

Abstract

The purpose of this study was to determine if depression interacted with the *apolipoprotein E* (*APOE*) gene to influence risk of dementia and rate of cognitive decline. Secondary analyses examined interactions between *APOE* and use of antidepressants. Adult Changes in Thought (ACT) is a prospective population-based cohort in an integrated health care delivery system. Initial recruitment occurred from 1994-1996 and 2000-2003, followed by continuous enrollment since 2004. The cognitive abilities screening instrument (CASI) was administered every two years to screen for dementia and was used to examine cognitive trajectory. For these analyses eligible participants had at least 10 years of enrollment in the health care system, *APOE* genotype, and valid CASI scores at baseline (N=3132, data through December 31, 2013). The primary exposure was time-varying depression, as measured by the CESD screening test and ICD-9 codes for major depression during office visits. Secondary analyses included antidepressant use as the exposure, by group: SSRIs (paroxetine vs. others), TCAs, SARIs, and Other, as a time-varying dichotomous variable such that participants were non-users until their first prescription, then users ever after, unless the first prescription occurred in the most recent year in order to avoid use related to prodromal symptoms. The independent variables were included with the exposure x APOE interaction term in all models. Dementia risk was analyzed using Cox proportional hazards models adjusted for age via the time axis, and for demographic characteristics, health behaviors, and health status. Analysis of cognitive trajectory used linear regression models with generalized estimating equations. During a mean follow-up of 7.9 years, 405 *APOE* ε4- participants (23.4%) developed dementia (259 (19.0%) Alzheimer's disease); 210 *APOE* ε4+ participants (34.0%) developed dementia (210 (27.6%) developed Alzheimer's disease). There was no statistically significant depression x *APOE* interaction, although individuals with both depression and the *APOE* ε4 allele together had higher dementia risk compared to APOE ε4- people with no depression (HR=2.60, 95% CI, 2.15, 3.68), which was a higher HR than either factor alone. A significant interaction between non-paroxetine SSRI use and

APOE was observed, such that *APOE* ε4+ individuals who took SSRIs had similar risk of dementia to *APOE* ε4- individuals who did not take SSRIs (HR=1.19, 95% CI, 0.83, 1.70). Results were similar for Alzheimer's disease. *APOE* did not interact with depression or antidepressant use to alter the rate of cognitive decline. Depression did not interact multiplicatively with *APOE* ε4 to influence risk of dementia and AD, while non-paroxetine SSRI use interacted with *APOE* to ameliorate the risk of dementia in *APOE* ε4+ individuals. Though exploratory, this observation has important clinical implications for a subset of individuals at increased risk of dementia and AD.

Introduction

Depression has been characterized as a risk factor for dementia and AD in multiple longitudinal studies [3–9], with a recent systematic review concluding that late-life depression is associated with a two-fold increased risk of dementia [10]. The mechanistic link between depression and AD is unclear, though several potential mechanisms have been hypothesized, including vascular disease, inflammatory changes, changes in glucocorticoid steroids and hippocampal atrophy, increased deposition of B-amyloid plaques, and nerve growth factor deficits (summarized in [5]). Additionally, late-life depression may also be an early symptom of dementia [9]. The ε4 variant of the *apolipoprotein E* (*APOE*) gene is a well-established genetic risk factor for dementia [36]. While a link between the *APOE* ε4 allele and depression itself is not well established in either AD patients or cognitively intact individuals [37], several recent studies suggest *APOE* ε4 may interact with depression synergistically to increase risk of dementia/AD [38–42] and to increase rate of cognitive decline in late life (reviewed in [43]). However, results of these studies were mixed; at this time no clear consensus exists in the literature on the existence or magnitude of such an interactive effect. Considering the individual influences on AD risk and cognition of both depression and *APOE* ε4, further study is warranted.

In the present study, we investigated the potential interaction between depression and *APOE* ε4 on dementia risk and cognitive decline using a population-based prospective cohort study with detailed information on depression, *APOE* genotyping information, and other covariates of interest. Additionally, treatment for depression may impact the interaction effects between *APOE* and depression. As the

participants in this cohort had a high frequency of antidepressant use in response to depressive symptoms, we used computerized pharmacy data to examine whether APOE status affected dementia risk and cognitive decline among individuals who used antidepressants (by class) in exploratory analyses.

Methods

Design, study setting, and participants

The parent study, Adult Changes in Thought (ACT), was undertaken to investigate, among other risk factors, the contributions to dementia risk of long-term use of a variety of commonly used medications. Study details have been described elsewhere [14]. Briefly, participants aged 65 and older were randomly sampled from Seattle area Group Health (GH) members, an integrated health care delivery system in the northwestern United States. The initial cohort included 2581 participants enrolled from 1994-1996, with an additional 811 participants enrolled in 2000-2003. Continuous enrollment has occurred since 2004 to replace those who developed dementia, died, or dropped out. Participants were assessed at entry and returned biannually to evaluate cognitive function and collect demographic characteristics, medical history, health behaviors, and health status. Dementia screening was performed using the Cognitive Abilities Screening Instrument (CASI), which evaluates multiple categories of cognitive function [18]. Diagnosis of dementia and AD was made by consensus conference using standard criteria [19], as described previously [14]. All subjects enrolled (and not withdrawn due to reasons other than death) in the ACT study with at least one follow-up visit, *APOE* genotyping, and 10 years of prior membership of GH at enrollment were included for the analyses of dementia and AD risk. Additionally, ICD-9 codes from office visits and therapy visits were used to exclude individuals diagnosed with bipolar disorder (using ICD-9 codes 296.5 and 296.6). For the cognitive trajectory analysis, visits during which a dementia diagnosis was obtained were not included; only subjects with a valid cognitive score at baseline were analyzed. Data through December 31, 2013, were included in these analyses.

Exposures

In order to assess presence or absence of depression over time, we used a combination of ACT data and GH office visit data. As depression is expected to vary over time (partially in response to

antidepressant medications administered), it was modeled as time-varying, such that at each ACT visit, indicators for depression were examined since the last visit and adjusted accordingly. ACT participants were administered the Center for Epidemiologic Studies Depression scale (CESD) at each biannual visit. The CESD is an effective screening tool for depressive symptoms; a score ≧ 10 was used as the threshold indicator for depression [23]. However, this score does not capture depression that occurred before the study period or in between study visits that resolved before the next study visit. Accordingly, ICD9-codes for major depressive disorder at GH office visits throughout the study period were also used as indicators for depression. The ICD-9 codes used were: 296.2x (major depressive disorder, single episode), 296.3x (major depressive disorder, recurrent episode), 311 (Depressive disorder, not elsewhere classified), and 300.4 (Dysthymic disorder). In addition to the time-varying depression variable that tracked depression throughout follow-up, a depression history at baseline variable was created. Individuals were identified as having depression history at baseline if either: CESD score ≧ 10 at study entry; or presence of an ICD-9 code for depression (as defined above) in the 10 years previous to baseline.

APOE genotype was collected at study entry for a subset (86%) of consenting ACT participants. Participants were characterized as *APOE ε4* positive if they had at least one copy of the ε4 allele, and were ε4 negative otherwise.

SSRIs were the most common therapies for depression in the ACT cohort by the end of the study period, though TCAs were commonly prescribed earlier and within the time frame of the ACT cohort study, allowing us to examine both major classes of antidepressants. Furthermore, because paroxetine has high anticholinergic activity [20], we grouped the other SSRI medications separately from paroxetine for analyses. Medication classes were grouped as follows: TCAs, SSRIs, Paroxetine, SARIs, and Other (which included the less commonly used NDRIs, NaSSA, SNRIs, MAOIs, and TeCASs). Prescription antidepressant use was identified from computerized pharmacy data, which included drug name, strength, route of administration, number of pills, and date dispensed. To avoid protopathic bias, we excluded prescriptions in the most recent 1-year period before each event. Protopathic bias occurs when a medication is inadvertently prescribed for an early manifestation (e.g., depression) of a disease (e.g., dementia) that has not yet been diagnostically detected. We created dichotomous variables that were

time-varying, such that a person was a non-user until their first prescription, then a user ever after. Exploratory analyses examined interactions between *APOE* and time-varying 10-year cumulative dose (in total standardized daily dosages, TSDDs) that was recalculated for the population at risk at each event through end of follow-up, as calculated in Chapter 1. The dosages were categorized as follows: 0=no use in previous 10 years; 1 = 1-365 TSDDs; 2 = 366-1095 TSDDs; and 3 = >1095 TSDDs.

For the cognitive trajectory analysis, individuals were non-users until their first prescription, then users ever after. Visits leading to a dementia diagnosis were excluded, since CASI scores at these visits were often so low that they would have strongly influenced results and reflected the dementia analyses, rather than showing patterns of cognitive decline in healthy aging individuals. Thus there was no need for accounting for protopathic bias by excluding recent prescriptions in this sample.

Outcomes

Participants underwent cognitive screening at baseline and every two years using the CASI, which has a range of 0-100 (higher scores indicate better performance). A score <86 triggered standardized diagnostic evaluation for dementia, which included physical and neurological examination and neuropsychological testing. Results and clinical data were reviewed by a multidisciplinary consensus conference and assigned dementia and AD diagnoses [19]. The date of dementia onset was assigned as the midpoint between the study visit that triggered the dementia evaluation and the preceding visit. Participants diagnosed with dementia were re-evaluated after one year to confirm diagnosis. In the cognitive trajectory analysis, we used the CASI score at each biannual visit.

Covariates

Covariate information was obtained from standardized questionnaires administered at each ACT study visit and Group Health electronic databases. Demographic factors included age, sex, race (white vs. non-white), and education (>12 years vs. <12 years). Participants provided self-reported history of diabetes mellitus, hypertension, and coronary heart disease (which included ever reporting MI, angina, CABG, angioplasty, stroke, TIA, or CEA). Self-reported health (poor or fair vs. good, very good, or excellent), smoking status (ever, never, or current), and exercise (15 minutes at least three times per

week) were also ascertained through questionnaires. Body mass index was measured at each ACT study visit, calculated as weight (kilograms) divided by height squared (meters), and categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (≥30 kg/m^2). For the dementia outcome analysis, a dichotomous indicator for baseline CASI score was included (≥92 vs. <92).

Statistical analysis

We used multivariable Cox proportional hazards regression models with participants' age as the time scale to estimate hazard ratios and 95% confidence intervals for the association between depression, *APOE ε4* and dementia or possible Alzheimer's disease. The interactions between depression and *APOE*, and between medication use and *APOE,* were examined by including the cross-product term and the independent variables in the same model. For the interaction analyses between *APOE ε4* and medication use, each interaction was tested in a separate model that included all other antidepressant classes without interactions (TCAs, paroxetine, other SSRIs, SARIs, and Other) in order to account for overlapping use and/or drug switching. Participants were censored at the earlier of their last ACT visit, disenrollment from Group Health, or death if they did not have a dementia diagnosis; all data before December 31, 2013 was included. In addition, for the AD analysis, subjects diagnosed with non-AD dementia were also censored at estimated onset of dementia. Separate models were fit for each outcome (all-cause dementia and possible AD). Antidepressant use and depression were modeled as time-varying measures. Values at study entry were used for all other covariates, which included age at study entry, sex, educational level, hypertension, diabetes, heart disease, smoking, BMI, CASI score, regular exercise, and self-reported health. We excluded observations with missing baseline covariate information (n=122).

For the cognitive trajectory analysis, we evaluated the average differences in rates of decline between depressed and non-depressed persons, or between user groups (with no use as the reference group for each antidepressant category) using linear regression models estimated via generalized estimating equations (GEE). GEE models account for repeated measures on individuals over time and provide a population-averaged approach, in order to investigate differences in population-averaged

responses. We used a working independence correlation matrix and calculated standard errors using the Huber-White sandwich estimators (the 'robust' option in STATA), in order to take into account issues concerning heterogeneity and lack of normality [25]. We estimated the average difference in rate of cognitive decline, defined as change in CASI score per year, by including an interaction term between age at follow-up and depression. Models were stratified by *APOE* status, and the interaction p-value was evaluated using a three-way interaction between depression, *APOE*, and age. In each interaction model, the independent variables were also included. The exploratory models examining medication use employed a similar strategy: the interaction between medication use and time were assessed in models stratified by *APOE*, while a three-way interaction between medication use, *APOE*, and age was used to obtain interaction p-values. Models were adjusted for the same covariates as the dementia/AD analyses. All analyses were performed with STATA SE 12 (StataCorp, College Station, TX, USA).

Results

In **Table 2.1,** we provide participant study characteristics at study entry by APOE status. The frequency of the ε4 allele in the ACT population (26% with at least one ε4 allele) is similar to the overall US population, in which 20-30% are estimated to have at least one e4 allele [44]. The mean age of the non-ε4 carriers at study entry was 75.2 years, which was a full year older than ε4 carriers. Carriers and non-carriers were not different in all other

Table 2.1. Baseline characteristics of participants[a] by *APOE* status

Characteristic	Non-ε4 carriers (n = 2127)	ε4 carriers (n = 762)	p-value
Age at entry, mean ± SD	75.2±6.4	74.2±5.9	<0.001
Male, n (%)	918 (43.2)	302 (39.6)	0.091
Nonwhite, n (%)	161 (7.6)	68 (8.9)	0.235
College education (n=2888), mean ± SD	1452 (68.3)	538 (70.6)	0.238
Obese (n=2830), n (%)	538 (25.9)	193 (25.8)	0.593
Depressed before or at entry[b], n (%)	441 (20.7)	160 (21.0)	0.878
Anxiety before or at entry, n (%)	169 (8.0)	62 (8.1)	0.868
CASI score at entry (n=2857), mean ± SD	93.8±4.5	93.7±4.7	0.631
Comorbid conditions at entry, n (%)			
Heart disease[c]	506 (23.8)	189 (24.8)	0.574
Diabetes mellitus (n=2885)	220 (10.4)	65 (8.5)	0.150
Hypertension (n=2867)	848 (40.2)	306 (40.5)	0.883
History of smoking (n=2883), n (%)	974 (45.8)	358 (47.2)	0.681
Fair or poor self-reported health (n=2887), n (%)	301 (14.2)	109 (14.3)	0.924
Regular exercise (n=3332), n (%)	1514 (71.3)	547 (71.9)	0.754
Antidepressant use[d]			
TCA, n (%)	509 (23.9)	179 (23.5)	0.807
Paroxetine, n (%)	82 (3.9)	31 (4.1)	0.795
Other SSRI, n (%)	193 (9.1)	66 (8.7)	0.732
SARI, n (%)	194 (9.1)	69 (9.1)	0.957
Other, n (%)	56 (2.6)	27 (3.5)	0.197
History of smoking (2883), n (%)	974 (45.8)	358 (47.2)	0.681
Fair or poor self-reported health (n=2887), n (%)	301 (14.2)	109 (14.3)	0.924
Regular exercise[e] (n=2885), n (%)	1514 (71.3)	547 (71.9)	0.754

[a]Only participants with two or more visits included, and must have enrolled in GHC at least 10 years before ACT entry. Individuals diagnosed with bipolar disorder excluded (n=24).
[b]Indicates a score of 10 or greater on the CESD, or an ICD9-code for depression at a previous office visit
[d]Heart Disease includes ever-reported MI, angina, CABG, angioplasty, stroke, TIA, or CEA
[d]All antidepressant prescriptions in the 10 years before ACT study entry were taken into account.
[e]Indicates at least 15 minutes of activity at least 3 times per week

demographics: greater than 90% were white, approximately 60% were women, and a majority had some college education. Antidepressant use was relatively low at study entry, with TCAs being the most-used antidepressant (24% in both groups), while other antidepressants, including SSRIs, were used by fewer than 10% of the participants (the high rate of TCA use compared to SSRI use is likely a reflection of the timing of the initial cohort enrollment from 1994-1996). However, by the end of the study period, the use of all antidepressants climbed, with non-paroxetine SSRI use doubling since study entry (**Table 2.2**). Overall, non-ε4 carriers and ε4-carriers were similar in demographics, health outcomes, and antidepressant use; however, ε4-carriers were slightly younger at baseline and had slightly shorter follow-up, reflecting the earlier mortality due to higher rates of dementia and AD seen in ε4-carriers (**Table 2.2**).

Table 2.2. Characteristics and outcomes of participants[a] according to *APOE* status during the study period

Characteristic	Non- ε4 carriers (n = 2127)	ε4 carriers (n = 762)	p-value
Duration of follow-up, years, mean ± SD	8.2±5.2	7.8±5.0	0.050
Ever depressed, n (%)	892 (41.9)	330 (43.3)	0.511
Ever anxiety, n (%)	275 (12.9)	116 (15.2)	0.112
Antidepressant use[a]			
TCA, n (%)	713 (33.5)	246 (32.3)	0.534
Paroxetine, n (%)	201 (9.5)	79 (10.4)	0.463
Other SSRI, n (%)	397 (18.7)	151 (19.8)	0.487
SARI, n (%)	392 (18.4)	130 (17.6)	0.399
Other, n (%)	127 (6.0)	44 (5.8)	0.844
Dementia dx	498 (23.4)	259 (34.0)	<0.001
AD dx (possible AD)	405 (19.0)	210 (27.6)	<0.001

[a]Only participants with two or more visits included, and must have enrolled in GHC at least 10 years before ACT entry. Individuals diagnosed with bipolar disorder excluded (n=24).
[b]Antidepressant prescriptions up to one year before event (censoring or dementia onset) included

The results of interaction analyses between *APOE* and depression are in **Table 2.3**, which shows results for interactions between *APOE* and depression history, defined as any depression by baseline ("Baseline Depression" in **Table 2.1**), and also between *APOE* and depression throughout the study as a time-varying covariate ("Ever Depression"). The reference group consisted of individuals who were non-ε4 carriers and had no depression. Compared to individuals who were *APOE* ε4- and no depression history by baseline, individuals with the ε4 allele (but no depression history) had an almost 2-fold increased risk of dementia (HR=1.77, 95% CI, 1.49, 2.11). Individuals without the ε4 allele but with a history of depression had a similar increase in risk compared to non-depressed, non-ε4 individuals (HR=1.63, 95% CI, 1.31, 2.02). Individuals with both the ε4 allele and a history of depression had a greater than 2-fold risk of dementia (HR=2.60, 1.92, 3.52), though the interaction between depression and

Table 2.3. Association between depression and dementia or AD by presence of *APOE* ε4

Model[a,b]	Dementia Events[c] N	Dementia HR (95% CI)	Dementia Int p-value[d]	Alzheimer's Events[c] N	Alzheimer's HR (95% CI)	Alzheimer's Int p-value[d]
Baseline[e]						
Depress-, ε4-	359	Reference		292	Reference	
Depress-, ε4+	199	1.77 (1.49, 2.11)		163	1.80 (1.48, 2.18)	
Depress+, ε4-	118	1.63 (1.31, 2.02)		195	1.63 (1.29, 2.08)	
Depress+, ε4+	49	2.60 (1.92, 3.52)	0.586	39	2.61 (1.86, 3.67)	0.587
Ever Depression[f]						
Depress-, ε4-	237	Reference		190	Reference	
Depress-, ε4+	141	1.80 (1.50, 2.18)		114	1.76 (1.44, 2.16)	
Depress+, ε4-	240	1.90 (1.56, 2.32)		197	1.80 (1.44, 2.26)	
Depress+, ε4+	107	2.81 (2.15, 3.68)	0.265	88	2.92 (2.18, 3.92)	0.665

[a]Adjusted for age (via the time-axis), cohort, gender, race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week). All models include the interaction term and the independent variables composing the interaction term.
[b]Each interaction model run separately
[c]Individuals in each category counted at time of event (final time point)
[d]Interaction p-value
[e]Defined as having CESD score ≥ 10 at study entry or having an ICD-9 code for depression within 10-year study period previous to study entry
[f]Time-varying depression variable, [d]efined as having CESD score ≥ 10 at an ACT visit and/or having an ICD-9 code for depression at a GH office visit

APOE was not statistically significant p=0.586. Results were similar for depression at any time during the study, and for AD.

The exploratory analyses examining the interactive effects of antidepressant use and *APOE* on risk of dementia and AD are in **Table 2.4**. Compared to individuals who were *APOE* ε4- and did not use TCAs, individuals with the ε4 allele (but no TCA use) had an almost 2-fold increased risk of dementia, as seen in all the models (HR=1.83, 95% CI, 1.51, 2.21). Individuals without the ε4 allele who were TCA users did not see a significant increased risk of dementia (HR=1.08, 95% CI, 0.88, 1.32). Individuals with both the ε4 allele and TCA use had an increased risk of dementia that was similar to the risk seen in individuals with the ε4 allele alone (HR=1.59, 95% CI, 1.23, 2.05). The interaction between *APOE* and TCA use was not statistically significant (p=0.189), nor was the interaction between *APOE* and SARIs (p=0.227). However, the interaction p-values for the SSRI groups were both statistically significant (non-paroxetine SSRI x *APOE* interaction p-value = 0.008, paroxetine x *APOE* interaction p-value = 0.023). However, the interactive effects between these two groups were quite different. Individuals with the ε4 allele (but no SSRI use) had an almost 2-fold increased risk of dementia, (HR=1.87, 95% CI, 1.58, 2.22). Non-ε4 carriers who used non-paroxetine SSRIs did not have an increased risk of dementia compared to non-ε4 non-SSRI users (HR=1.12, 95% CI, 0.87, 1.46). However, SSRI use in ε4 carriers reduced the risk

Table 2.4. The association between antidepressant use and dementia/AD by presence of *APOE* ε4

	Dementia			Alzheimer's		
Model[a,b]	Events[c] N	HR (95% CI)	Int p-value[d]	Events[c] N	HR (95% CI)	Int p-value[d]
TCA						
TCA-, ε4-	289	Reference		233	Reference	
TCA-, ε4+	166	1.83 (1.51, 2.21)	.	140	1.91 (1.54, 2.36)	.
TCA+, ε4-	188	1.08 (0.88, 1.32)	.	154	1.11 (0.89, 1.39)	.
TCA+, ε4+	82	1.59 (1.23, 2.05)	0.189	62	1.48 (1.11, 1.99)	0.055
SSRI use						
Other SSRI						
SSRI-, ε4-	382	Reference		314	Reference	
SSRI-, ε4+	211	1.87 (1.58, 2.22)	.	172	1.88 (1.56, 2.27)	.
SSRI+, ε4-	95	1.12 (0.87, 1.46)	.	73	0.91 (0.68, 1.22)	.
SSRI+, ε4+	37	1.19 (0.83, 1.70)	0.008	30	0.93 (0.62, 1.38)	0.010
Paroxetine						
PX-, ε4-	405	Reference		329	Reference	
PX-, ε4+	221	1.82 (1.54, 2.15)	.	181	1.83 (1.52, 2.19)	.
PX+, ε4-	72	1.90 (1.43, 2.52)	.	58	2.20 (1.62, 2.99)	.
PX+, ε4+	27	1.99 (1.31, 3.00)	0.023	21	2.16 (1.35, 3.45)	0.024
SARI						
SARI-, ε4-	385	Reference		309	Reference	
SARI-, ε4+	211	1.77 (1.49, 2.09)	.	172	1.78 (1.48, 2.15)	.
SARI+, ε4-	92	0.84 (0.65, 1.08)	.	78	0.82 (0.63, 1.08)	.
SARI+, ε4+	37	1.14 (0.80, 1.63)	0.227	30	1.06 (0.71, 1.57)	0.169

[a]Adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously), age (via the time-axis), cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week). All models include the interaction term and the independent variables composing the interaction term.
[b]Each interaction model run separately
[c]Individuals in each category counted at time of event (final time point)
[d]Interaction p-value

of dementia so that it was not significantly different from the reference group of non-ε4 carriers without SSRI use (HR=1.19, 95% CI, 0.83, 1.70). Similarly, the risk of dementia was similar in paroxetine-using ε4 carriers and paroxetine-using non-ε4 carriers; however, in both cases, paroxetine use was associated with an almost two-fold increased risk of dementia compared to non-ε4 carriers and non-paroxetine users (HR=1.90, 95% CI, 1.43, 2.52 for non-ε4 carriers who used paroxetine; HR = 1.99, 95% CI, 1.31, 3.00 for ε4 carriers who used paroxetine).

Exploratory analyses examining interactions between APOE and 10-year dosage categories showed similar patterns (**Table 2.5**). Due to small numbers of individuals in each category after stratification, results were not as robust as seen in the dichotomous medication use analyses, particularly for paroxetine users who were ε4 carriers (as indicated by very large confidence intervals around the estimates). Lighter use of non-paroxetine SSRIs (1-365 TSDDs and 366-1095 TSDDs) appears to be driving the interaction, while heaviest non-paroxetine SSRI use may not provide similar amelioration of risk for ε4 carriers.

Table 2.5. The association between antidepressant use by 10-year dosage category and dementia/AD by presence of *APOE* ε4

	Dementia			Alzheimer's		
Model, TSDD[a,b]	Events[c] N	HR (95% CI)	Int p-value[d]	Events[c] N	HR (95% CI)	Int p-value[c]
TCA						
TCA-, ε4-	326	Reference		267	Reference	
TCA-, ε4+	178	1.78 (1.48, 2.14)	.	149	1.83 (1.49, 2.24)	.
TCA+, ε4-						
1-365	80	0.97 (0.75, 1.24)	.	64	0.95 (0.72, 1.26)	.
366-1095	26	1.26 (0.83, 1.90)	.	23	1.38 (0.89, 2.15)	.
1095+	45	1.34 (0.97, 1.85)	.	33	1.23 (0.85, 1.79)	.
TCA+, ε4+						
1-365	38	1.82 (1.30, 2.56)	0.798	28	1.65 (1.11, 2.44)	0.818
366-1095	11	1.28 (0.69, 2.36)	0.137	9	1.32 (0.67, 2.59)	0.113
1095+	21	1.60 (1.01, 2.51)	0.155	16	1.55 (0.92, 2.60)	0.246
SSRI use						
Other SSRI						
SSRI-, ε4-	385	Reference		316	Reference	
SSRI-, ε4+	214	1.87 (1.58, 2.21)	.	175	1.88 (1.56, 2.26)	.
SSRI+, ε4-						
1-365	43	1.07 (0.77, 1.49)	.	30	0.91 (0.61, 1.34)	.
366-1095	14	1.22 (0.70, 2.12)	.	14	1.47 (0.84, 2.56)	.
1095+	35	1.30 (0.89, 1.90)	.	27	1.21 (0.79, 1.86)	.
SSRI+, ε4+						
1-365	20	1.12 (0.70, 1.78)	0.042	15	1.02 (0.60, 1.76)	0.130
366-1095	4	0.89 (0.33, 2.41)	0.102	4	1.07 (0.39, 2.89)	0.099
1095+	10	1.55 (0.82, 2.95)	0.231	8	1.50 (0.73, 3.07)	0.311
Paroxetine						
PX-, ε4-	409	Reference		333	Reference	
PX-, ε4+	223	1.83 (1.55, 2.16)	.	183	1.86 (1.55, 2.23)	.
PX+, ε4-						
1-365	41	1.72 (1.22, 2.43)	.	33	1.78 (1.22, 2.61)	.
366-1095	15	3.07 (1.79, 5.25)	.	10	2.60 (1.36, 4.98)	.
1095+	12	2.16 (1.20, 3.91)	.	11	2.40 (1.29, 4.46)	.
PX+, ε4+						
1-365	19	2.23 (1.38, 3.58)	0.229	15	2.27 (1.33, 3.87)	0.250
366-1095	3	1.22 (0.39, 3.84)	0.018	2	1.08 (0.27, 4.39)	0.057
1095+	3	1.23 (0.39, 3.86)	0.074	2	0.96 (0.24, 3.90)	0.049
SARI						
SARI-, ε4-	399	Reference		321	Reference	
SARI-, ε4+	217	1.75 (1.48, 2.07)	.	176	1.78 (1.48, 2.14)	.
SARI+, ε4-						
1-365	52	0.87 (0.65, 1.17)	.	44	0.92 (0.66, 1.27)	.
366-1095	13	0.99 (0.56, 1.74)	.	10	0.95 (0.51, 1.81)	.

[a]Adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously), age (via the time-axis), cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week). All models include the interaction term and the independent variables composing the interaction term.
[b]Each interaction model run separately
[c]Individuals in each category counted at time of event (final time point)
[d]Interaction p-value

Depression slightly increased the rate of cognitive decline, though the differences in rates

between non-depressed and depressed individuals were not statistically significant (**Table 2.6**). Among non-ε4 carriers who were not depressed, the rate of decline was approximately 0.11 points per year (meaning the mean CASI score among this group decline by 0.11 points per year; 95% CI -0.13, -0.10; negative values indicate declining rates, positive point values indicate increasing rates). Depression increased the rate of decline by 0.03 points per year (95% CI -0.06, 0.01), so that the total rate of decline for depressed individuals who were non-ε4 carriers was 0.14 CASI points per year (95% CI, -0.17, -0.11). The decline among depressed individuals was not statistically different than the decline among non-depressed individuals (interaction p-value for depression x time not shown). Similarly, for non-depressed ε4 carriers, the mean rate of cognitive decline was 0.12 points per year (95% CI, -0.14, -0.10). Like the

Table 2.6. Mean CASI score difference per year between users and non-users, and total rate of change (in CASI score) for each group, stratified by APOE status

	APOE ε4-		APOE ε4+		
Model[a,b]	**Mean difference in change in CASI score per year (CI)**	**Mean total point change in CASI per year (CI)**	**β_3: Mean difference in change in CASI score per year (CI)**	**Mean total point change in CASI per year (CI)**	**Interaction p-value**[c]
No depression	Reference	-0.11 (-0.13, -0.10)	Reference	-0.12 (-0.14, -0.10)	0.840
Depression+	-0.03 (-0.06, 0.01)	-0.14 (-0.17, -0.11)	-0.02 (-0.08, 0.04)	-0.14 (-0.20, -0.09)	
No TCA	Reference	-0.10 (-0.13, -0.08)	Reference	-0.14 (-0.18, -0.09)	0.324
TCA+	-0.01 (-0.05, 0.02)	-0.12 (-0.13, -0.10)	0.01 (-0.03, 0.06)	-0.12 (-0.09, 0.12)	
No Other SSRI	Reference	-0.11 (-.0.14, -0.09)	Reference	-0.12 (-0.016, -0.09)	0.550
Other SSRI+	-0.004 (-0.03, 0.03)	-0.12 (-0.13, -0.10)	-0.01 (-0.05, 0.04)	-0.13 (-0.16, -0.10)	
No Paroxetine	Reference	-0.12 (-0.14, -0.10)	Reference	-0.12 (-0.16, -0.09)	0.362
Paroxetine+	0.01 (-0.02, 0.04)	-0.11 (-0.13, -0.09)	-0.004 (-0.05, 0.04)	-0.13 (-0.16, -0.09)	
No SARI	Reference	-0.12 (-0.14, -0.10)	Reference	-0.13 (-0.16, -0.09)	0.597
SARI+	0.01 (-0.02, 0.04)	-0.11 (-0.13, -0.09)	0.001 (-0.05, 0.04)	-0.13 (-0.16, -0.09)	

[a]Adjusted for all other time-varying antidepressant class use (all antidepressant classes analyzed simultaneously), age (via the time-axis), cohort, gender, depression (time-varying), race, education (some college vs none), and baseline variables including: age, dichotomized CASI score, comorbid vascular disease (including cardiovascular disease, hypertension, and diabetes), body mass index category, history of cigarette smoking, self-rated health (fair/poor vs better), and regular exercise (15 minutes at least 3 times per week). All models include the interaction term and the independent variables composing the interaction term.
[b]Each interaction model run separately
[c]Interaction p-value from the three-way interaction between the exposure (depression or antidepressant use), APOE, and time

non-ε4 carriers, depression increased the rate of cognitive decline slightly among ε4 carriers by 0.02 points per year, for a total mean decline per year of 0.14 points (-0.20, -0.09); this increase was not statistically significant. There was no significant interaction between *APOE* and depression that affected the rate of cognitive decline (p-value for three-way interaction between *APOE*, depression, and time = 0.840). Similarly, antidepressant use did not statistically significantly change the rate of cognitive decline compared to non-users (antidepressant use x time interaction p-values not shown), nor did rates of decline differ significantly by *APOE* status (3-way interaction p-values shown in **Table 2.6**).

Discussion

Depression is an established risk factor for dementia and AD. We sought to determine whether *APOE* ε4 modified this association using a population based longitudinal cohort with detailed covariate data and time-varying indicators for depression. We did not find evidence for a statistically significant multiplicative interaction between either history of depression and *APOE*, or between time-varying depression throughout the study period and *APOE*, though individuals with both depression and the ε4 allele had non-significantly increased risk of dementia and AD compared to individuals having either depression alone or the ε4 allele alone. Depression did not significantly affect cognitive decline over time, nor did the *APOE* ε4 allele modify the association between depression and cognitive decline. Interestingly, in exploratory analyses, we observed strong interactions between SSRI use and *APOE*, such that SSRI use equalized the risk between ε4 carriers and non-carriers. Specifically, ε4-carriers who used non-paroxetine SSRIs had dementia and AD risk that was similar to non-ε4 carriers, indicating that non-paroxetine SSRI use mitigated the high risk attributable to the ε4 allele. The equalizing effect was observed between paroxetine and *APOE* as well, though risk of dementia remained high in both ε4 carriers and non-carriers. Antidepressant use did not alter the course of cognitive decline, nor did *APOE* modify the relationship between antidepressant use and cognitive decline.

Previous studies have investigated the combined effects of depression and *APOE* ε4. Four studies observed a pattern indicating a modifying effect of *APOE* ε4 individuals with depression, such that individuals with at least one ε4 variant and depression had an increased risk of dementia and AD compared to non-depressed, non-ε4 individuals [38,40–42], though only two of these studies showed a

statistically significant interaction between *APOE* ε4 and depression [38,40]. However, several important limitations should be noted. One of these studies included men only [38] and may not be generalizable, as the effect of *APOE* on dementia and AD risk may be more pronounced in women [45]. Additionally, in that population, the ε4 allele frequency was relatively low (17.6%) and the dementia incidence was also relatively low (from 4.2% in the group lacking the depression and ε4 risk factors, to 13.7% in the group with both risk factors). While larger datasets are more efficient at discerning real statistical associations, small datasets are at risk for unstable risk estimates and false positives, so should be regarded with caution. The other study showing statistical significance for an interaction between depression and *APOE* ε4 included women [40], but had a very short follow-up time of approximately 2.4 years, and thus is at risk of detecting depression as a symptom of dementia, which would inflate the perceived effect of an interaction between depression and *APOE*. The study authors replicated their initial results in another study population, though the methods were nearly identical, including the short follow-up time [46].

The other two published studies found a non-significant interaction between *APOE* and depression though results showed increased dementia risk for individuals with both risk factors compared to individuals without either risk factor [41,42]. These findings were similar to our results, though study populations were much smaller than ours (n=405 and 142, respectively).

An additional study sought to specifically examine the temporal effects of depression and *APOE* ε4 on dementia/AD risk [39] and observed that recent depression (within 10 years of diagnosis) was associated with dementia and AD regardless of *APOE* status; however, a significant interaction was detected between *APOE* status and depression more than 10 years before onset of dementia, such that distal depression (> 10 years before onset) was associated with risk of dementia only among ε4 carriers. An additional exploratory study in this dataset showed this increased risk for dementia in ε4 carriers persisted whether individuals were treated or untreated.

Similar inconsistencies are seen in studies assessing the same interaction on cognitive decline. Several studies indicate a synergistic interaction between depression and *APOE* on cognitive decline, such that individuals with both *APOE* and depression had faster rates of cognitive decline [43,47,48], though other studies did not report similar findings [49]. It should be noted that the joint effect of *APOE* and depression is more likely to affect rate of cognitive decline, but not overall cognitive status in healthy

individuals, as shown in a large detailed cross-sectional study [50]. Studies with larger sample sizes and longer follow-up times were more likely to detect a statistically significant interaction between depressive symptoms and *APOE* status, as confirmed by a large prospective cohort study of community-dwelling adults over 65 years (n=4150) followed up for an average of 9.1 years. This study showed an interaction between depressive symptoms (evaluated by the CESD) and *APOE* ε4 on cognitive decline (measured by a battery of 4 tests) over time. We did not observe a statistically significant interaction effect of depression and *APOE* on cognitive decline in the ACT cohort. However, the CASI is likely to have high ceiling effects, as many participants in the ACT cohort were achieving maximum or near maximum scores at baseline. Additionally, the CASI is a screening tool, and as such may not be sensitive enough to detect differences over time, especially in those individuals performing at high cognitive functioning.

We undertook additional exploratory analyses to examine interactions between *APOE* and antidepressant use on dementia and AD as an extension of the depression and *APOE* analyses initially hypothesized. Individuals in the ACT cohort had a high rate of uptake of antidepressant medications (almost half the cohort, 48.6%, had at least one antidepressant medication by end of the study period, as stated in Chapter 1). While many antidepressant medications are for indications other than depression (such as anxiety and insomnia), we hypothesized that antidepressant uptake itself may be another indicator of depression, as well as a potential confounder, since successful treatment of depression may serve to obscure the findings in the primary analyses. Intriguingly, we observed a strong interaction between non-paroxetine SSRI use and *APOE*, such that SSRI use appears to mitigate the risk effect of the ε4 allele on dementia and AD. To our knowledge, no other study has explicitly examined this interaction on dementia outcomes. The only study we could find examining interactions between antidepressant use and *APOE* genotypes, for any outcome, compared mirtazapine to paroxetine efficacy (for depression remission) in cognitively intact elderly depressed patients [51]. This study found a differential effect by *APOE* status, such that among mirtazapine users, ε4 carriers had faster remission of depression symptoms than non-ε4 carriers. This effect was reversed in paroxetine users: ε4 carriers had slower remission than non-ε4 carriers.

Other studies examining a variety of environmental and lifestyle risk factors have observed similar interactions with *APOE*, in which the disease risk attributable to the ε4 allele is mitigated by healthy

behaviors, demographics, or interventions. *APOE* likely interacts with a variety of other genetic and environmental variables to impact risk of AD. Since *APOE* is functionally involved in cholesterol transport and lipid distribution, the interaction between *APOE* and vascular risk factors on dementia and AD risk is of particular interest. Interestingly, several studies reported evidence for an interaction between *APOE* genotypes and exposures traditionally related to vascular health, such as physical activity, that showed a potential amelioration of risk specifically for ε4 carriers. For instance, one recent study found that the risk of dementia among ε4 carriers with high education, high leisure activity score, and without vascular risk factors was the same as the dementia risk in non-ε4 carriers; additionally, these three factors seemed to delay dementia onset such that ε4 and non-ε4 carriers had similar dementia-free survival time [52]. Several recent studies have pointed to comparable risk-reducing interactive effects between the ε4 allele and lifestyle and environmental factors on multiple outcomes, including dementia [53,54] brain atrophy and activation [55–57], lipid response [58–60], beta-amyloid burden [61], and cognition [62,63], though other studies did not find interactions [64,65]. Such effects may explain why *APOE* ε4 is a poor predictor of both dementia and cardiovascular outcomes, despite strong associations with dementia, AD, and CVD risk in the overall population.

While the underlying biology of an interaction between non-paroxetine SSRI use and *APOE* on dementia is unknown, a study investigating the interaction between lifestyle factors and *APOE* on cognitive performance [62] built on a previously described neurocognitive plasticity framework [66] in this context. In brief, plasticity refers to the potential for improvements in cognition through acts of training, practice, or experience; such activities may serve to preserve or enhance various aspects of cognitive performance with aging, and may be influenced by genetics. Under this theory, perhaps non-SSRIs increase cognitive plasticity in ε4 carriers by treating the underlying risk factor (depression), or through inherent neurogenic properties of SSRIs that are more effective in ε4 carriers [67,68]. These mechanisms are still poorly understood, and more study is required to understand the effects of antidepressants on healthy and depressed brains, in non-ε4 carriers and ε4 carriers.

Our study had several limitations. While the ACT cohort itself is one of the largest longitudinal study populations tracking older adults in this detailed manner, only a subset consented to genetic testing for *APOE*; as interaction analyses require stratification of populations, the numbers of individuals in

certain strata became small, and may have resulted in loss of statistical power to detect associations. Another limitation is the potential misclassification of confounders, particularly depression. Patients prescribed an antidepressant are much more likely to receive an ICD-9 code for depression than subjects not started on antidepressants. Thus, we may have failed to detect individuals with depression who were not treated, or who were treated with psychotherapy. As noted above, the CASI may be insufficiently sensitive to detect changes in cognition in healthy, cognitively intact individuals who are already performing at a high level. Lastly, since the ACT cohort is a relatively homogeneous group of people in a relatively small geographical area, generalizability may be limited.

Our study also had many strengths. The ACT study is one of the largest and most detailed of its kind. Computerized pharmacy records enabled us to fully characterize dosage and duration of medications in greater detail than comparable studies, and allowed us to discern between not only medication classes, but also individual medications themselves; few previous studies examining cognitive outcomes associated with antidepressant use separated the highly anticholinergic paroxetine from the other SSRIs. Additionally, participants in the cohort were enrolled and followed for longer than most studies evaluating AD risk and cognition over time (8-9 years on average). Pertinent health data was recorded at each biannual visit, allowing us to include multiple covariates in our study that are often overlooked, though some residual confounding may still occur. Depression was accounted for over time through multiple methods (CESD screening and office visits), rather than through self-report or simply at baseline. Careful biannual cognitive screening allows for timely diagnosis capture and the ability to track trends in cognition over time. Additionally, timely diagnoses of AD and dementia allow us to take into account symptoms and medications prescribed due to prodromal symptoms.

While we did not observe a multiplicative interaction between depression and APOE ε4, individuals with both risk factors did have an overall increased risk of dementia. Such findings may have implications for clinicians who seek to manage depression in older adults, particularly if genetic results become available. Effective treatment for depression in individuals with the ε4 allele will be especially important to avoid or delay onset of dementia and AD. Additionally, our exploratory findings observing a mitigation of the ε4-associated risk among individuals using non-paroxetine SSRIs could have important implications for the at-risk group of older adults with ε4. However, as this was a post-hoc exploratory

study with a yet-to-be-determined mechanism of action, more research is needed to determine the full scope of this potential effect before clinical action is taken.

Chapter 3

Genotype-driven recruitment for *APOE ε4*: practical and ethical considerations

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, the primary cause of disability in the elderly. Approximately 5 million Americans age 65 and over were estimated to have AD in 2014, a number that is predicted to rise to 13.8 million by 2050 [69], with the current lifetime risk of AD dementia for a 65-year-old estimated to be at 10.5% [70]. The cause of late-onset AD is still not fully understood, and is likely a complex interplay between genetics, environment, and health and lifestyle factors. The idea that AD risk could be decreased by potentially modifiable risk factors has gained traction in recent years. One-third to one-half of AD cases might be attributable to potentially modifiable risk factors, including physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes, low educational attainment, and depression [71,72]. In light of the devastating personal and economic burden of AD, targeting the midlife factors that contribute to this disease could lead to important interventions to ameliorate risk or delay onset. Indeed, several randomized controlled studies are currently under way in Europe and the U.S. to assess interventions targeted at some of these risk factors [73,74].

Despite the current focus on modifiable risk factors, a subset of individuals has an underlying genetic, and therefore non-modifiable, risk factor for AD. While many genetic variants associated with varying degrees of risk of late-onset AD (LOAD) have been identified, only the ε4 variant of the *apolipoprotein E* (*APOE*) gene has been consistently associated with increased risk over decades of study in multiple populations. However, while the association between the ε4 allele and AD is strong and replicable, it has also been observed that the ε4 allele is not necessary to cause AD, nor is it determinative. It is unknown why some individuals with ε4 never progress to disease, or whether interventions for modifiable risk factors would impact ε4 carriers similarly to the rest of the population. Recent studies indicate an intriguing interaction between *APOE ε4* and several lifestyle interventions, such that individuals with the ε4 allele may experience a differential effect of the intervention compared to individuals who do not carry the ε4 allele. This chapter explores a hypothetical research study in which just such an intervention is tested under a model employing genotype-driven recruitment, with an

emphasis on the ethical considerations involved in designing a study focused on a well-known harmful genetic variant.

APOE background and interactions

APOE normally plays a role in lipid transport, including shuttling cholesterol to neurons in healthy brains. Notably, *APOE* has a role in beta amyloid (Aβ) metabolism, and while the exact mechanism is unknown, the ε4 variant appears to accelerate neurotoxic Aβ accumulation, aggregation, and deposition in the brain [75]. *APOE* was initially studied for its relation to cardiovascular disorders and lipid metabolism [76], though the ε4 variant is also now known as a risk factor for Alzheimer's disease (AD) and other neurodegenerative disorders and has been studied extensively in this research area since the early 1990s. *APOE* is polymorphic, with three common alleles (ε2, ε3 and ε4). The ε3 allele is most prevalent, with about 60% of the US population carrying two copies, while only 10-20% of the US population carries at least one copy of the ε2 allele. At least one copy of ε4 is found in 20-30% of the US population, while only 2% of the US population carries two copies of ε4 [44]. These frequencies vary across racial and ethnic groups, with African Americans having a higher frequency of the ε3/ε4 genotype (26-28%) compared to Caucasian Americans (~18%) and Asians (14-19%) [76]. For the purposes of this discussion, we will focus on the Caucasian allele frequencies, as the analyses proposed here will examine a cohort that is of predominantly Caucasian ethnicity [14]. The ε2 form is thought to decrease risk of AD, while the ε4 form has been shown in multiple studies to increase risk of AD, with a gene dose-dependent pattern: carrying one copy increases the risk of developing AD 2-4 fold relative to ε3/ε3 homozygotes in Caucasian populations, while carrying two copies may increase the risk of AD up to 16-fold in Caucasian populations [77].

APOE likely interacts with a variety of other genetic and environmental variables to impact risk of AD. One burgeoning area of research involves examining interactions between *APOE* and lifestyle factors such as education, diet, and exercise on risk of AD. Since *APOE* is functionally involved in cholesterol transport and lipid distribution, the interaction between *APOE* and vascular risk factors on AD risk is of particular interest. Intriguingly, several studies reported evidence for an interaction between *APOE* genotypes and exposures traditionally related to vascular health, such as physical activity, that shows a

potential amelioration of risk specifically for ε4 carriers. For instance, one recent study found that the risk of AD among ε4 carriers with higher levels of education, higher leisure activity scores, and without vascular risk factors was the same as the AD risk in non-ε4 carriers; additionally, these three factors seemed to delay dementia onset such that ε4 and non-ε4 carriers had similar dementia-free survival time [52]. Several recent studies have pointed to similar risk-reducing interactive effects between the ε4 allele and lifestyle and environmental factors on multiple outcomes, including dementia [53,54] brain atrophy and activation [55–57], lipid response [58–60], and cognition [62,63], though other studies did not find interactions [64,65]. If lifestyle factors do indeed modify risk of AD in ε4 carriers differentially, clinicians could use this information to tailor interventions to those patients at high AD risk due to *APOE ε4*. However, due to heterogeneity in defining outcomes and exposures, small sample sizes, and heterogeneous populations, more study is needed to clarify the extent of the clinical effect of interactions between lifestyle factors and *APOE ε4*.

If future observational studies confirm a beneficial association between *APOE ε4* and certain modifiable lifestyle factors, such an interaction would be difficult to test under controlled conditions. The lifestyle and demographic factors in the observational studies cited, which include diet, physical exercise, education, cognitive activity, and leisure activity, are difficult to define and measure, and often impossible to control. However, the previous dissertation chapters have highlighted an intriguing and highly testable interaction that may reduce the risk of AD associated with *APOE ε4*. In brief, the use of non-paroxetine SSRIs (fluoxetine, sertraline, or citalopram) appears to reduce the risk of AD and dementia in ε4 carriers, such that SSRI+ and ε4+ individuals experienced the same overall risk of dementia and AD as individuals without SSRI treatment or the ε4 allele. Additionally, SSRI treatment appears to slow the accelerated cognitive decline seen in ε4 carriers to rates similar to non-ε4 carriers. Though the effect is seemingly strong, this is only one study and as of yet has not been replicated in other observational cohorts. However, given the ability to carefully and precisely administer the intervention (unlike other factors such as diet, education, or physical activity), and given the relative safety of the non-paroxetine SSRIs, this is an intervention that could be tested in a randomized controlled trial. Additionally, given the reduction in statistical power that occurs when examining gene x environment interactions, and the length of time needed to follow the participants to endpoint, the study population could be carefully selected from

previously existing longitudinal cohorts in which genetic testing has already taken place in order to increase the frequency of individuals carrying the ε4 allele. Such a strategy has been previously described as "genotype-driven recruitment [78,79]," and entails a careful consideration of the ethics involved in participant recruitment, as well as decisions surrounding the disclosure of genetic results to research participants in the course of such recruitment.

Genotype-Driven Recruitment background

The explosion of genomic research in the last decade has led to an accumulation of biobanks and databases that provide researchers with seemingly unlimited research opportunities. Typically, a genomic research study entails recruiting research participants with a known clinical phenotype, and if the genetic variant of interest is rare, large numbers of participants must be screened in order to obtain enough individuals with both the condition and the rare variant for study. This can be quite expensive and time-consuming, and may be a limiting factor in obtaining enough statistical power to further understanding of the functional significance of a given variant under study. Genotype-driven recruitment (GDR), in contrast, is a study design in which researchers invite participants from an existing research study with specific genotype(s) of interest to participate in another study aimed at elucidating phenotypic, and related measurable, correlates of the genotype [79,80]. Such a design can maximize the utility of information already collected in previous genomic studies in order to save valuable resources and increase statistical power, particularly in the case of rare variants, gene x environment interactions, or outcomes that require long follow-up times, such as dementia.

While GDR is potentially a powerful tool in genomic research, a special set of ethical challenges arise in its application [78,79]. The primary concerns surround the issue of disclosure of genetic results to research participants during recontact: what, if anything, should they be told about the genotype that led to the invitation to participate in additional research [79]? General ethical recommendations regarding the return of individual results to research participants specify that results should only be disclosed if the benefits of disclosure outweigh the risks, usually through a careful weighing of the clinical utility and validity of a given genetic test [81,82]. At the same time, maintaining trust and transparency with participants is crucial for continued participation. An NIH-sponsored workshop consisting of multiple

stakeholders (including genomic researchers and study coordinators, research participants, clinicians, bioethics scholars, experts in human research protections, and government representatives) was convened to discuss the ethical issues surrounding GDR. The working group issued key recommendations for researchers going forward with this study design that attempts to balance prior thinking about result return with the special obligations entailed by GDR [78]. The recommendations resulting from this workshop include:

1. Researchers should disclose the possibility of future contact for further research recruitment during the informed consent process for the initial study;
2. Researchers should consider offering participants a choice at the time of initial consent about future contact for further research recruitment;
3. Contact about additional research should be made by a person or entity known to the participant;
4. The process for contacting participants about additional research should be designed based on a range of considerations related to the research team and study question;
5. Thresholds established for the return of individual genetic research results in general should not be used for decision-making about return of results in the context of genotype-driven recruitment;
6. In most cases, individual genetic research results should be offered in the context of genotype-driven recruitment. A careful series of steps should be used both to avoid leaving prospective participants uninformed about the purpose of the study and to maximize their right not to know unwanted genetic information; and
7. For each study, appropriate approaches to genotype-driven recontact and the disclosure of individual genetic research results should be determined by researchers in consultation with their IRB.

Going forward, these recommendations can help researchers to not only make crucial decisions during a GDR study, but also to increase awareness of these issues during the informed consent procedures of the parent study in order to more easily facilitate GDR in the future as new research questions arise.

Since the following hypothetical study involves recontacting participants enrolled in a long-term longitudinal study, satisfying the recontact requirements would be less difficult than for single-contact cross-sectional studies. For instance, such participants would be less likely to be surprised by being recontacted, as they have interacted with study researchers multiple times over a period of years, and have demonstrated a commitment to research by continuing to participate. For the purposes of this discussion, we will focus on issues surrounding return of genetic research results in the context of GDR, and will assume that the appropriate recontact procedures, as outlined in recommendations 1-4, have been followed. We will also assume that no participants have been informed of their *APOE* status previously, in accordance with standard guidelines [83,84].

Hypothetical study proposal: implementing GDR from a longitudinal parent study

To date, discussions of GDR study designs have focused primarily on recruiting participants from two types of parent study: phenotype-driven studies, in which the participants either have a given health condition, or are aware that they (or their family members) are at risk of a health condition; and studies involving collection of genetic material from healthy volunteers, such as biobanks [85,86]. In these discussions, GDR was used to recruit participants with a rare genetic variant of uncertain significance, which is the primary purpose and power of GDR designs. However, GDR can also be a powerful tool when considering the great expense and complexity of studies that require long follow-up times but the genotype of interest is not rare, such as studies examining genetic risk factors for dementia and cognitive decline. If a genetic variant of interest were to be studied in this context, having the ability to select individuals who are currently enrolled in a longitudinal parent study maximizes the use of the resources already invested, while starting a new cohort would require a large investment of resources and time. Additionally, only the individuals who qualify for the intervention need to be recontacted, as the outcomes under study are already being followed up in the existing cohort from which control subjects can be selected.

Another unique aspect of the proposed study is that the genotype under consideration (*APOE ε4*) is perhaps the most widely studied gene variant in the literature, rather than a rare variant of uncertain significance. Information about risk of CVD and AD due to *APOE ε4* is widely available, and individuals

who are recontacted for an *APOE ε4* study may make erroneous assumptions about their status and risk of disease, even if they do not ultimately choose to participate in the GDR study and if results are not disclosed. This requires a careful consideration of the GDR recommendations surrounding return of genetic results.

Since the interaction between non-paroxetine SSRI use and *APOE ε4* has not been observed in more than one study at this time, the proposed study should be considered hypothetical, and as such, many specifics will remain open to further amendment as new results are uncovered. For the time being, the goal is to start a considered discussion of the ramifications of such a study, as it sheds a unique perspective on the ongoing debate regarding the disclosure of *APOE* genetic results [87,88].

The primary aim of the hypothetical study is to test the hypothesis that SSRI use ameliorates the risk of dementia and AD attributed to the *APOE ε4* allele. A brief description of the study population and methods is outlined below. The ethical considerations during recruitment will be discussed in the next section.

Participants: Adult Changes in Thought (ACT) Study

A GDR design will be implemented in one or more currently operating population-based longitudinal cohorts. The model study we will use as an example here is the Adult Changes in Thought (ACT) study [14], though other longitudinal cohorts examining cognition and dementia could be approached to increase recruitment numbers. However, study participants identified for recruitment must satisfy several key requirements for inclusion: cognitive testing at baseline and at regular follow-up intervals (via MMSE, CASI, or related test), regular assessment for dementia and AD, and inclusion of baseline demographic data including (at minimum) gender, race, education, and presence or absence of vascular health conditions (heart disease, hypertension, and diabetes).

The Adult Changes in Thought (ACT) study [14] was undertaken to investigate, among other risk factors, the contributions to dementia risk of long-term use of a variety of commonly used medications. Through Group Health's electronic medical records and extensive pharmacy database, information on a wide range of covariates, health conditions, and medications (including pre-ACT enrollment medication information for long-term GHC members) is available over an extended period of time [15]. The ACT

cohort currently includes nearly 4,000 participants who were evaluated biannually for cognitive decline and dementia, from 1994-2013. Dementia screening was performed using the Cognitive Abilities Screening Instrument (CASI), which evaluates multiple categories of cognitive function [18]. Diagnosis of AD and non-AD dementia was made by consensus conference using standard criteria [19], as described previously [14]. Depressive symptoms were also assessed using the Center for Epidemiologic Studies Depression scale (CESD) at each biannual visit.

All participants for the proposed intervention will be initially identified based on their *APOE* status. As of December 31, 2013, 3,386 ACT participants had been genotyped for *APOE*: 2,490 individuals, or 73.5%, were not ε4 carriers. Of the remaining 896 (or 26.5%), 772 (22.8%) were ε3/ε4, 51 (1.5%) were ε4/ε4, and the remaining 73 (2.1%) were ε2/ε4. Equal numbers of participants with at least one ε4 allele (*APOE ε4+*) and those without an ε4 allele aged 65 or greater with no history of depression or antidepressant use in the previous 10 years, and no dementia/AD at baseline, will be recruited for the intervention.

Inclusion criteria and intervention

Given an overall AD incidence of 28% among *APOE ε4+* individuals in the ACT cohort, with effect size HR=0.6 to be tested (as seen in dissertation chapter 2), sample size calculations indicate that a minimum of 430 *APOE ε4+* individuals must be included (with 215 assigned to the intervention) to perform a Cox proportional hazards survival model with alpha = 0.5 and power = 0.8 (calculations performed in STATA v.12). The intervention under study would be 12-18 months of the minimum effective geriatric daily dose of fluoxetine, sertraline, or citalopram, depending on doctor preference and patient tolerance. If a patient experiences adverse effects resulting in adherence issues, switching to another of these three medications would be allowed in order to minimize drop-out. Half the *APOE ε4+* participants would be randomized to the intervention, while the other half would be followed up as usual in their respective cohort (for ACT, cognitive assessments and demographic questionnaires every two years). An equal number of non-ε4 participants will also be randomized. Thus, only the 215 *APOE ε4+* and 215 *APOE ε4-* individuals who will be administered the intervention will need to be recontacted for recruitment. The ACT data that are routinely obtained at biannual visits will allow us to identify both *APOE ε4+* controls

who are not depressed or on antidepressants, as well as *APOE ε4*- controls who are not depressed or on antidepressants for post-hoc comparisons (these individuals make up the majority of the ACT cohort, providing a much larger than necessary pool of control individuals). For the survival analysis, a minimum of six years of follow-up is optimal, while cognitive changes can be assessed every two years by the study researchers. A Data Safety and Monitoring Board (DSMB) should also assess all outcomes at two-year increments. Per DSMB guidelines, the study will be terminated early if there are serious concerns about patient safety and adverse outcomes, or if benefit is clearly evident (i.e. if statistical analyses strongly confirm the findings of Chapter 2).

Statistical analysis

For the survival analysis comparing incident dementia and AD between the treated and untreated groups, we will use the Cox proportional hazards model assessing time to dementia and AD using age as the time axis. Subjects will be followed up through their last ACT visit. Baseline covariates will include age, gender, race, education, presence of vascular co-morbidities, and cognitive test scores.

For the rate of cognitive decline analysis, we will use a generalized estimating equations (GEE) model to determine the rate of change in CASI scores per year within each of the four treatment groups. The first analysis could occur within two years of baseline for preliminary findings, then be updated biannually as participants continue testing at each biannual ACT visit. The longitudinal model will incorporate the same covariates as were used in the survival analysis to control for confounding.

GDR for *APOE ε4*: to tell or not to tell

While the tailoring of clinical interventions to individuals based on genetics has become a sort of "holy grail" of personalized/precision medicine, it is important to keep in mind some specific issues surrounding genetic testing for *APOE ε4*. As discussed previously, while it is known that the ε4 allele is associated with a greater risk of AD and of developing AD at a younger age (particularly in homozygotes) [89], the ε4 allele is not necessary to cause AD (i.e. not all people with AD have the ε4 allele), nor is it determinative (i.e. not all people with the ε4 allele will develop AD). In order to evaluate the utility of *APOE* as a tool to not only aid in diagnosing AD, but also to predict AD in asymptomatic persons, in 1995

the joint American College of Medical Genetics (ACMG) and American Society of Human Genetics (ASHG) Test and Technology Transfer committee developed a 10-member ACMG/ASHG Working Group to assess available data on the association of AD with *APOE* alleles. Their findings were summarized in a statement which recommended against the use of *APOE* testing for AD diagnosis and prediction due largely to deficits in clinical utility, predictive/diagnostic value, and insufficient benefit of such knowledge, given that at this time there is no proven intervention to avoid AD, or cure for those already afflicted [84]. The recommendations against clinical genetic testing of the gene have remained largely unchanged in the 20+ years since issued; in fact, as recently as July 2015, the American College of Medical Genetics specifically recommended against *APOE* testing as a predictive test for AD in the list of "Five Things Patients and Providers Should Question," as part of the Choosing Wisely initiative (http://www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/). This serves as the starting point for the ethical considerations involved in our proposed GDR study.

Recommendations for ethical approaches to GDR advocate a lower threshold of disclosure than that which is generally acceptable [78]. A number of national ethical guidelines regarding individual result return affirm the importance of clinical validity and utility of any result considered for disclosure [82,90,91], a bar that is clearly not met by *APOE* according to the ACMG and ASHG. However, within the context of GDR, offering individual results is less a matter of clinical benefit, and more about performing ethically responsible research by respecting participants' desire to know, and avoiding obfuscation of the underlying reason for recruitment. But can we apply this lowered threshold to disclosure of *APOE* results?

There is already controversy about this question in the context of both consumer genetic testing and primary research studies. In contrast to the recommendations of the ACMG and ASHG, and fears that *APOE* testing of asymptomatic individuals might do more harm than good given low clinical utility and an association with a stigmatized disease such as AD, some researchers have advocated for disclosure of *APOE* results within certain contexts, pointing to the supposed value of "personal utility" of testing, rather than clinical utility [88]. Additionally, patients themselves appear increasingly interested in knowing their *APOE* status. Direct-to-Consumer (DTC) genetic testing companies, such as 23andMe, offered *APOE* testing and risk assessment for AD until the FDA suspended DTC risk-assessment reports pending further inquiry (https://www.23andme.com/health/); uptake of the test prior to the FDA suspension is

unknown. Furthermore, a number of studies have examined attitudes of the general population toward *APOE* testing, and found that a majority of people had a high interest in being tested if it was offered to them [92], with rates of interest approximately the same whether the individual had a family history of AD or not [93]. The primary reasons for *APOE* testing cited by study participants were: to provide information for future planning and arrangement of personal affairs; altruism and making a research contribution; to organize long-term care; and to potentially learn about one's own children's risk via their own risk assessment [87,88].

The notion that personal utility should be considered in addition to clinical utility would not be complete without mentioning the much-discussed results of the Risk Evaluation and Education for Alzheimer's disease Study (REVEAL) which examined psychosocial and behavioral effects of *APOE* testing, and found that individuals who test positive for the ε4 allele did not experience adverse psychological effects to the degree anticipated [87]. It should be noted that individuals in the REVEAL study were a self-selected group of individuals who were highly motivated to seek testing and who received genetic counseling before and after being tested. Results should therefore probably not be generalized to the wider population and, in particular, may not predict the response of research participants for whom individual genetic results were not expected. These studies do, however, highlight the difficulties in disclosing complicated risk information that is probabilistic in nature, and indeed, question whether such information is truly meaningful to recipients. For example, in a follow-up REVEAL study that examined attitudes among individuals who received their *APOE ε4* genetic information, approximately half of the participants who were able to correctly recall their risk information after six weeks of testing still believed their own pretest perceptions of risk, whether or not their perceptions were the same as the risks suggested by testing [94].

At this time, ACMG clinical practice guidelines do not recommend disclosure of *APOE ε4* results for prediction of AD, despite discussions provoked by REVEAL study findings concerning personal utility and low adverse psychological impact of testing [83]. However, in the research milieu, *APOE* results can be (and have been, as shown in the REVEAL studies) disclosed as long as appropriate protections are in place, particularly with respect to a patient's right NOT to know the results of genetic testing. It is possible that results of APOE can be disclosed during the recruitment of the proposed study, and careful

consultation with the IRB should be undertaken to ensure adequate protections. In the context of GDR, the challenge will be to avoid inadvertent disclosure of genetic results during the recruiting process. This leaves open the question of how to recruit participants for the proposed *APOE ε4* study without obfuscating the purpose of the study while simultaneously avoiding disclosure during recruitment.

What do we say to the individuals being recruited to avoid inadvertent disclosure?

To determine the most ethical course of action for recruiting participants for a study focused on *APOE ε4* and dementia risk, it is worth examining the attitudes of research participants themselves. Research participants who were recontacted for earlier studies with a GDR design had a diverse range of opinions regarding the disclosure of their own genetic results [85,86]. Reactions to questions about disclosure of individual genetic results from the parent study during the recruitment process for the further research varied according to the study population. Healthy volunteers who contributed to biobanks had more concerns about the risks associated with disclosure than individuals who had been diagnosed, or were related to someone who had been diagnosed, for a given condition that was being studied [85]. A striking finding was that a majority of participants thought that researchers should offer individual results despite uncertain clinical validity and utility [85], as the participants perceived that "knowledge is power," even if there wasn't anything they could currently do with the results that might be returned. This points to the fact that many participants make assumptions about their genetic risk and disease etiology that may not be true, despite detailed information letters and conversations with recruiters. Indeed, the act of recruitment caused anxiety in several participants, and they wondered if they'd been contacted due to "something freaky going on with my genes," as one participant stated [86].

If we consider our proposed study, which will return genetic results of a known disease-linked risk variant, we need to be especially careful to respect the participants' right not to know without being deceptive about the purpose of recontacting them [78]. An information letter to recruit them into an *APOE* intervention study could, for example, inadvertently or erroneously alert participants that they are *APOE ε4+*. One way to avoid this risk would be to send a recruitment letter to all genotyped ACT participants that is explicit about recruiting individuals who are both *APOE ε4+* and *APOE ε4-*. Such a letter would contain a brief description of the study under consideration, and clearly inform each recipient that ALL

genotyped participants had been contacted whether they are *APOE ε4*+ or not, and if they wish to be considered for inclusion in the study, they will be subject to further screening regarding past antidepressant use and *APOE* status. This information letter will need to state plainly that if they agree to participate further, they will have the option to receive their *APOE* genetic information. Contact information for further questions should be provided to all participants before agreeing to pursue the study further. A detailed framework for communicating genetic risk (by genetic counselors), as outlined in the REVEAL studies [95], will need to be established as well.

It should be noted that ACT participants who had already consented to *APOE* testing in the parent study were aware that their *APOE* status would be determined but not disclosed in the course of the original research, so they may be less likely to make assumptions about their *APOE ε4* status or to feel deceived during the pre-recruitment phase. However, this assumption underlies the importance of stressing the fact that the participants can continue to have the right not to know their genetic results if they choose to participate in the intervention study.

Conclusions

The genotype-driven recruitment (GDR) strategy described here would allow researchers to maximize use of a valuable resource, the long-term longitudinal cohort. This study seeks to determine whether a specific intervention could ameliorate the increased risk of AD and dementia experienced by *APOE ε4* carriers, and would be the first study to test the hypothesis that non-paroxetine SSRIs might be used off-label to reduce the AD risk of ε4 carriers. Ethical considerations suggest that we can disclose individual genetic results of this type in the context of GDR, which typically has a lower bar for disclosure of genetic results. Care must be taken in order to avoid inadvertently disclosing *APOE* status during the recruitment process by emphasizing that all individuals receiving a pre-recruitment information letter have an equal chance of NOT having the genetic variant under study. Researchers must be as transparent as possible to minimize the perception of deception during the recruitment process, though patient populations who have already been tested for *APOE* in a parent study will be familiar with the reasons for non-disclosure from their first consent process, and may have fewer concerns about researchers “hiding” important information from them. While the standard recommendations for non-disclosure of *APOE*

genetic results should be upheld in most research contexts, if the results of this study show that the intervention ameliorates risk of dementia and AD in ε4 carriers, then a case could be made that genetic testing for *APOE ε4* has a new dimension of previously unseen clinical utility, and guidelines for testing could be revisited.

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