

1 **Sex and APOE genotype influence AD neuropathology but not epigenetic age across**
2 **diagnosis**

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34 **Abstract**

35 **Introduction:** Alzheimer's disease (AD) disproportionately affects females. We determined
36 whether physiological biomarkers (neuroplasticity, immune, stress, epigenetic) explain why
37 females are more susceptible to AD than males using the Alzheimer's Disease Neuroimaging
38 Initiative (ADNI) database.

39 **Methods:** Using the complete ADNI cohort, we analysed the effect of sex and APOE genotype
40 (number of ε4 alleles) and sex and diagnosis (cognitively normal (CN), mild cognitive
41 impairment (MCI), AD) on (1) AD related endpoints: memory scores, executive function scores,
42 hippocampal volume, cerebrospinal fluid (CSF) amyloid beta, tau and p-tau; (2) markers of the
43 immune system (interleukins, C-reactive protein, and immunoglobulins), neuroplasticity
44 (intercellular adhesion molecule, ICAM1), and stress (cortisol); and (3) epigenetic age.

45 **Results:** Females had higher levels of tau and p-tau compared to males and increasing alleles of
46 APOEε4 disproportionately increased tau and p-tau compared to males. Females had larger
47 hippocampal volume (corrected with intracranial volume) and better memory scores (that include
48 verbal memory) than males, regardless of APOE genotype and diagnosis. There were also sex
49 differences in biomarkers with females having higher levels of plasma C-reactive protein and
50 lower levels of CSF IL-8, IL-16, immunoglobulin A, and ICAM1. We did not observe an
51 association between sex, diagnosis, or APOE genotype and blood epigenetic age acceleration or
52 intrinsic epigenetic age acceleration.

53 **Conclusion:** In females tau pathology was increased but memory scores were higher and
54 corrected hippocampal volume were larger compared to males suggesting females have a reserve
55 against brain damage that delays either the onset of cognitive decline or diagnosis. In this ADNI
56 cohort more males than females were diagnosed with MCI but with no significant difference in

57 AD diagnosis, although more females presented with AD, suggesting the progression from CN,
58 MCI to AD may be sex-specific. We found sex differences in immune biomarkers indicating that
59 the underlying physiology may participate in differential aging with and without a diagnosis of
60 AD or MCI between the sexes.

61

62 **Keywords:** Sex differences, inflammation, epigenetic age, hippocampus

63

64 **Introduction**

65 Alzheimer's disease (AD) is a neurodegenerative disease characterized by severe
66 cognitive decline (Alzheimer's Association, 2017). Modifiable risk factors associated with AD
67 include stress (Caruso et al., 2018), sociocultural or lifestyle factors (e.g., education, marital
68 status, exercise), and conditions (diabetes, obesity, and cardiovascular disease; Baumgart et al.,
69 2015; Nebel et al., 2018; Xu et al., 2015). Non-modifiable risk factors include age, biological
70 sex, and APOE genotype (Riedel et al., 2016). Females are more likely to be diagnosed with AD
71 in Europe and Asia, although this sex difference may depend in part on geographic location as
72 the sex difference is not always observed in studies from the United States (reviewed by Ferretti
73 et al., 2018; Mielke et al., 2014; Nebel et al., 2018). Nevertheless, regardless of prevalence,
74 females show greater neuropathology (brain atrophy, neurofibrillary tangles) and cognitive
75 decline with AD than males in both Europe and the United States (Ardekani et al., 2016; Barnes
76 et al., 2005; Holland et al., 2013; Hua et al., 2010; Irvine et al., 2012; Koran and Hohman, 2017;
77 Lin et al., 2015).

78 The hippocampus is one of the first brain areas to show atrophy with AD (Apostolova et
79 al., 2006; Jack et al., 2000; Kidron et al., 1997) and hippocampal atrophy correlates with
80 cognitive decline (Petersen et al., 2000) and AD pathology (neurofibrillary tangles; Jack et al.,
81 2002). Previous studies using the Alzheimer's Disease Neuroimaging Initiative (ADNI) indicate
82 that females have greater atrophy rates and cognitive decline than males with AD (Holland et al.,
83 2013; Hua et al., 2010; Lin et al., 2015). However, there is limited research into the role of sex in
84 the possible mechanisms underlying AD. In addition, few studies have examined the interaction
85 of genetic polymorphisms and biological sex in AD. The ε4 allele of the APOE gene is a well-
86 known genetic risk factor of AD (Corder et al., 1993) and is associated with accumulation of
87 amyloid beta protein (Ossenkoppele et al., 2015). In females between 65 and 75 years, one allele
88 of ε4 increases the risk of AD by 4-fold relative to males, indicating that the APOE genotype
89 affects males and females differently (meta-analysis by Neu et al., 2017). Understanding why
90 females are at a higher risk and have a higher burden of the disease is important for the
91 development of tailored treatments based on sex and genetics.

92 Chronic inflammation is a hallmark of AD, as evidenced by increased expression of
93 proinflammatory cytokines in the brains of AD patients which can exacerbate AD pathology
94 (Heppner et al., 2015; Kinney et al., 2018; Swardfager et al., 2010). There are sex differences in
95 immune responses (Klein and Flanagan, 2016) which can affect neuroplasticity (Dantzer, 2018;
96 de Miranda et al., 2017) and interact with stress (Dantzer, 2018), but it is not known how these
97 may be related to sex differences in AD. Biomarkers are highly sought after to predict disease
98 onset and progression and to understand the possible underlying mechanisms of AD to develop
99 better treatments. Therefore, the first objective of this study was to investigate potential

100 physiological biomarkers (neuroplasticity, immune, stress) that may explain sex differences in
101 AD and in people at risk for AD using the ADNI database.

102 Aging biomarkers also include epigenetic alterations, and these have been associated with
103 a variety of pathologies and adverse health conditions, including normal cognitive aging and
104 neurodegenerative phenotypes such as AD (Hannum et al., 2013; Horvath, 2013; Levine et al.,
105 2015; Yokoyama et al., 2017). Recently, molecular biomarkers of aging known as “epigenetic
106 clocks” have been developed based on DNA methylation signatures (Hannum et al., 2013;
107 Horvath, 2013). Epigenetic age or “DNAmAge” is a measure of the biological age of a sample
108 (cell or tissue), and can be calculated across a range of tissues and time points, providing an
109 accurate estimation of a sample’s chronological age based on the presence or absence of
110 methylation at the 5’ carbon of informative CpG dinucleotides throughout the human genome
111 (Horvath, 2013). Positive deviations of epigenetic age from chronological age (positive
112 epigenetic age acceleration) reflect more rapid biological aging and have been associated with
113 numerous factors including smoking, obesity, Parkinson’s disease, Trisomy 21, and cancer (Gale
114 et al., 2018; Horvath, 2013; Horvath et al., 2015; Horvath and Ritz, 2015), while negative
115 deviations of epigenetic age from chronological age (negative epigenetic age acceleration) have
116 been associated with high life-expectancy populations and memory retention (Degerman et al.,
117 2017; McEwen et al., 2017). In AD, epigenetic age acceleration of the frontal cortex was
118 associated with amyloid load, neuritic plates, and cognitive decline (Levine et al., 2015). Intra-
119 individual DNA methylation profiles in peripheral tissue are correlated with the epigenetic
120 signature in the brain, likely due both to identical genetic background affecting DNAm, and
121 common signatures of epigenetic aging (Braun et al., 2019), thus it is reasonable to hypothesize
122 that epigenetic age acceleration may also be detectable in peripheral tissues such as blood in AD

123 participants. In healthy individuals, aging males exhibit more positive epigenetic age
124 acceleration than females in blood and buccal tissue, and multiple brain regions (Horvath et al.,
125 2016); in AD and other diseases with a sex difference, it is possible that the underlying sex-
126 specific pathological mechanisms may be reflected in epigenetic age acceleration measures – for
127 example, in AD females could potentially have more positive epigenetic age acceleration than
128 males.

129 Our aims were to first examine sex differences in cognitive ability, volume of the
130 hippocampus, neuropathological markers of AD and the potential underlying physiological
131 mechanisms (neuroplasticity, immune, stress) and how these may be affected by APOE genotype
132 (number of ε4 alleles), and secondly by dementia status (cognitively healthy (CN), mild
133 cognitive impairment (MCI), AD). Our third objective was to investigate epigenetic age in
134 peripheral tissue of CN, MCI and AD participants, and to study the relationship between sex,
135 APOE genotype, dementia status, and epigenetic age acceleration.

136

137 **Methods**

138 *ADNI database*

139 Data used in the preparation of this article were obtained from the Alzheimer's Disease
140 Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in
141 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner,
142 MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging
143 (MRI), positron emission tomography (PET), other biological markers, and clinical and
144 neuropsychological assessment can be combined to measure the progression of mild cognitive

145 impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see
146 www.adni-info.org. Data used in this article were downloaded on or before Jan 16, 2019.

147

148 *Statistical Methods: Sex and APOE genotype and sex and diagnosis*

149 We included all participants that had a baseline diagnosis in the ADNI database (total n =
150 1,460, n= 630 females, n=830 males). Data included in our analyses were: demographics (age,
151 years of education, and ethnicity), baseline diagnosis (cognitively normal, CN; early MCI,
152 EMCI; late MCI, LMCI; or AD), number of APOE ε4 alleles (0, 1 or 2), ADNI executive
153 function Z-scores, ADNI memory Z-scores (using data from the ADNI neuropsychological
154 battery and validated in Crane et al., 2012; Gibbons et al., 2012), hippocampal volume (mm³),
155 cerebrospinal fluid (CSF) amyloid beta (pg/ml), CSF tau (pg/ml), and CSF p-tau (pg/ml). The
156 executive function score included WAIS-R Digit Symbol Substitution, Digit Span Backwards,
157 Trails A and B, Category Fluency, and Clock Drawing (Gibbons et al., 2012). The composite
158 memory score included Rey Auditory Verbal Learning Test, AD Assessment Schedule -
159 Cognition, Mini-Mental State Examination, and Logical Memory data (Crane et al., 2012). A
160 small subset of participants also had inflammatory markers measured in CSF (N = 279), and
161 plasma (N = 527) listed in Table 2A. Hippocampal volume was divided by intracranial volume to
162 correct for differences in brain size, as sex differences in hippocampal volume are influence by
163 intracranial volume (Lotze et al., 2019; Tan et al., 2016) and is presented as a ratio.

164 We compared all available data for each study variable between the sexes using the
165 Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.
166 We used general linear models to determine the relationships between (1) sex and APOE
167 genotype or (2) sex and dementia diagnosis and cognitive ability, corrected hippocampal volume,

168 and biomarkers. All models included age as a covariate. To test the main question, all models
169 initially included an interaction between sex and APOE genotype or sex and dementia diagnosis;
170 if this interaction was not significant, it was removed from the model to estimate the main effects
171 of sex and APOE genotype or diagnosis. Significance was based on the likelihood ratio test, and
172 all p-values for comparisons of sex and either APOE or diagnosis for all outcomes combined
173 were corrected for multiple testing using the Benjamini-Hochberg false discovery rate method
174 (Benjamini and Hochberg, 1995). All regression analyses were carried out in R v3.5.1 (R Core
175 Team 2018).

176

177 *Statistical Methods: Epigenetic Age*

178 We used DNAm data quantified with the Illumina Infinium HumanMethylationEPIC
179 BeadChip array (“EPIC” array) for 1905 blood samples from 640 unique ADNI participants
180 (n=284 females, n= 356 males; Vasanthakumar et al., 2017) with CN, MCI and AD diagnosis.
181 DNAm IDAT files were read into R v3.5.1 (R Core Team, 2018) using the ‘minfi’ package, and
182 annotated with the most recent version of the EPIC manifest, the Infinium MethylationEPIC v1.0
183 B4 Manifest File, (available from <https://support.illumina.com/downloads.html>) (Aryee et al.,
184 2014; Fortin et al., 2017). We excluded 11 low quality samples from 9 unique participants from
185 further analyses on the basis of having a median methylated or unmethylated probe intensity
186 <10.5 (Aryee et al., 2014; Fortin et al., 2017), the remaining samples were background
187 normalized and dye-bias adjusted with normal exponential out-of-band (“noob”) normalization
188 (Triche et al., 2013). DNAm data were converted to beta values and biological sex for all
189 samples was confirmed by clustering samples on all DNAm probes mapping to the X and Y
190 chromosomes. Beta values were calibrated to Horvath’s 21,368-probe training dataset, and

191 epigenetic age was calculated using R code modified for compatibility with the EPIC array using
192 the 334/353 epigenetic clock probes present on the array from <https://horvath.genetics.ucla.edu/>
193 (Horvath, 2013; Teschendorff et al., 2013). The missing DNAme values at these CpG sites can
194 also be imputed based on the k-nearest neighbors method. We observed a very high correlation
195 between epigenetic age values calculated with the missing probes removed versus imputed with
196 k=10 (R=0.99, p<2.2e-16), in agreement with previous reports; we therefore chose to remove
197 missing probes (Fiorito et al., 2017; McEwen et al., 2018).

198 Prior to statistical analyses we removed all technical replicates. Epigenetic age
199 acceleration was calculated as the residual of epigenetic age regressed on chronological age and
200 technical/batch covariates, including the laboratory collection site at which blood samples were
201 drawn, and EPIC microarray chip and row. Intrinsic epigenetic age acceleration, a measure
202 designed to be independent of age-related changes in whole blood cell-type proportions, was
203 calculated as described in Chen et al. (Chen et al., 2016) as the residual of epigenetic age
204 regressed on chronological age, technical covariates of collection site, row, and chip, and the
205 proportions of six blood cell types (CD8T, CD4T, NK, B cells, monocytes, and granulocytes)
206 estimated from noob-normalized methylation data with the Houseman algorithm (Houseman et
207 al., 2012). For participants who contributed more than one blood DNAme sample within the 2-
208 year collection period, we determined that longitudinal data collected within the median 3.6-year
209 error of the epigenetic clock could not be meaningfully evaluated, and therefore calculated mean
210 epigenetic age acceleration measures per participant from all available time points and performed
211 all statistical analyses on these mean values.

212 Statistical analyses of epigenetic age acceleration were conducted using data from the
213 remaining 640 participants (see Table 2B). To determine if epigenetic age acceleration or

214 intrinsic epigenetic age acceleration differed by sex, dementia diagnosis, or APOE genotype, we
215 used unbalanced two-way ANOVA designs. With CSF biomarker (amyloid beta, tau and p-tau)
216 data available from the ADNI repository for a smaller subset of participants with matched EPIC
217 DNAme data, (n=533, see Table 2C) we used linear regression to test whether APOE ϵ 4
218 genotype, amyloid beta, tau, p-tau, dementia diagnosis, or sex were significantly associated with
219 epigenetic age acceleration.

220

221 **Results:**

222 *Demographic and biomarker information*

223 Table 1 gives a summary of the variables for the overall data set (N=1460). Overall,
224 females were significantly younger and had fewer years of education than males (P<0.0001 for
225 both). There were more white males than white females in our sample and there were more non-
226 white females compared to non-white males (P<0.05). In terms of APOE genotype, there were
227 no sex differences in distribution of APOE genotype with 11% females and 12 % of males
228 possessing two alleles of APOE ϵ 4. In the overall data set, the proportion of participants in each
229 of the diagnosis categories was significantly different for females and males (P<0.05). There
230 were more females with a baseline diagnosis of AD compared to males (23.7% compared to
231 21.7%, unadjusted P = 0.41), although not significantly, and more females were cognitively
232 normal than males (26.7% compared to 20.8%, unadjusted P = 0.01). However, there were more
233 males with a diagnosis of late MCI (39.5% versus 32.5%, unadjusted P=0.007) and early MCI
234 (18.0% versus 17.1%, unadjusted P=0.74) compared to females, although not significantly.

235 Because not all data were available for each subject we created a summary table for the
236 participants: with CSF biomarkers (Table 2A; N=279), with whole blood EPIC DNAme data

237 (Table 2B; N=640) and with matched EPIC data and measured CSF biomarkers (Table 2C;
238 N=533). Among those with measured CSF biomarkers, demographics were very similar as per
239 results from overall data set in Table 1(see legend of Table 2). For the data applicable to the
240 participants with available EPIC DNAm data (Table 2B) and participants with EPIC DNAm
241 data and CSF biomarkers (Table 2C), most of the demographics were similar to the entire data
242 set except the proportion of participants in each of the diagnosis categories was not significantly
243 different between females and males.

244 In the overall data set, females had a smaller uncorrected hippocampal volume but larger
245 corrected hippocampal volume, greater CSF amyloid beta, tau and p-tau, and higher memory
246 function z-scores than males (Table 1). Biomarkers in the CSF were measured in a subset of
247 participants (Table 2A). In this smaller cohort, females and males had similar levels of CSF
248 CRP, CD 40 antigen and IL-6 receptor. However, females had lower CSF cortisol, interleukin-3,
249 interleukin 8, interleukin-16, immunoglobulin A, and intercellular adhesion molecule compared
250 to males (Table 2A).

251

252 *Sex and APOE genotype are associated with changes in memory, hippocampus volume, AD and*
253 *CSF inflammatory markers*

254 Our first aim was to investigate whether sex and APOE genotype interact to influence
255 cognitive ability, volume of the hippocampus, and biomarkers of AD and inflammation. There
256 were significant interactions between sex and APOE ϵ 4 genotype for CSF tau, p-tau, and IL-16
257 (Table 3). Tau and p-tau levels were significantly higher in females with one or two alleles of
258 APOE ϵ 4 compared to males (Fig 1 A and B). Although CSF p-tau and tau levels also increase in
259 males with APOE ϵ 4 genotype, they do not rise to the same extent as in females. IL-16 levels

260 were significantly lower in females with no APOE ϵ 4 alleles compared to males, whereas levels
261 were similar between the sexes with one or two APOE ϵ 4 alleles (Fig 1 C and D).

262 Both sex and APOE genotype were independently (main effects of sex or APOE
263 genotype) associated with memory z-scores and corrected hippocampal volume (Table 3).
264 Females had higher memory z-scores and larger corrected hippocampal volume across all APOE
265 genotypes (Fig 1 E and F). Lower memory z-scores were associated with increasing number of
266 APOE ϵ 4 alleles in both sexes. Similarly, corrected hippocampus volume was significantly lower
267 with increasing number of APOE ϵ 4 alleles in both sexes. Increasing APOE ϵ 4 alleles was also
268 associated with lower executive function z-scores, lower amyloid beta, and lower C-reactive
269 protein (Table 3; Fig 1 G-I), however there was no additional association of these variables with
270 sex. Finally, results were similar for biomarkers in plasma (Supplementary Table S3).

271

272 *Sex and diagnosis are associated with changes in memory, hippocampus volume, AD and CSF*
273 *inflammatory markers*

274 We next tested whether sex and dementia status (CN, MCI, and AD) influenced cognitive
275 ability, corrected hippocampal volume, and CSF biomarkers of AD and inflammation. There
276 were no significant interactions between sex and diagnosis for any of the tested variables
277 (memory, executive function, corrected hippocampal volume, CSF tau, p-tau, amyloid beta, and
278 CSF and plasma inflammatory markers). However, overall both sex and diagnosis were
279 independently associated with memory z-scores, corrected hippocampal volume and CSF tau and
280 p-tau (Table 4). Females had higher memory scores, larger corrected hippocampus volume, and
281 higher tau and p-tau compared to males, irrespective of diagnosis. As expected, increasing

282 severity of diagnosis was associated with lower memory and executive function scores, smaller
283 corrected hippocampus volume, and higher CSF tau and p-tau irrespective of sex (Fig 2 A-D).

284 We found that although females had higher CSF levels of interleukin 16 (IL-16), and
285 lower levels of interleukin 8 (IL-8), immunoglobulin A (IgA), and intercellular adhesion
286 molecule 1 (ICAM1), controlling for age, compared to males, there was no association between
287 these variables and diagnosis (Fig 2 E-H). Finally, there were associations between diagnosis and
288 executive function z-scores, and amyloid beta, controlling for age, but not between these
289 variables and sex (Fig 2 I and J).

290 The results for biomarkers and inflammatory markers in plasma were similar
291 (Supplementary Table S4), with the exception of a significant relationship between plasma C-
292 reactive protein (CRP) and sex (adjusted p=0.03), and also between plasma cortisol and baseline
293 diagnosis (adjusted P=0.01; Fig 2 K and L). Males have lower levels of CRP compared to
294 females and we observed a trend between diagnosis and CRP levels in plasma with lower CRP
295 levels in late MCI and AD (adjusted P=0.08). Plasma cortisol was lower in late MCI compared
296 to CN but higher in AD compared to CN. In summary, although we detected associations
297 between sex and diagnosis and various parameters, we did not find evidence for a clear sex and
298 diagnosis interaction.

299

300 *Epigenetic age, sex, dementia diagnosis, and AD biomarkers*

301 We investigated the hypothesis that sex and dementia diagnosis affect epigenetic age
302 acceleration in blood samples of ADNI participants (see Table 5).

303 Epigenetic age acceleration was not associated with sex, dementia diagnosis (CN, EMCI,
304 LMCI, and AD), or the interaction of sex and diagnosis after multiple test correction (Figure 3).

305 Intrinsic epigenetic age acceleration was also not significantly associated with participant sex,
306 diagnosis, or their interaction term.

307 To assess the effect of sex and more broadly defined dementia-associated cognitive
308 impairment on epigenetic age acceleration, we compared epigenetic age acceleration between
309 participants with any form of clinically ascertained cognitive impairment (AD + LMCI + EMCI,
310 n=423, proportion female 41%) and those without (CN, n=217, proportion female 50%). By two-
311 way unbalanced ANOVA neither sex, dementia status, nor their interaction were significantly
312 associated with epigenetic age acceleration after correction for multiple comparisons.

313 Matched biochemical data including APOE ϵ 4 genotype and CSF concentrations of
314 amyloid beta, tau, and phosphorylated tau was available for a subset of participants with EPIC
315 DNAm data (n=533). Based on the hypothesis that epigenetic age acceleration may be more
316 strongly associated with concentrations of pathologically relevant compounds than with
317 diagnosis, we assessed the impact of sex, APOE ϵ 4 genotype, amyloid beta concentration, tau and
318 p-tau concentration on epigenetic age acceleration and intrinsic epigenetic age acceleration with
319 linear regression. None of these variables was significantly associated with epigenetic age
320 acceleration (Table 6, results for intrinsic epigenetic age acceleration not shown).

321 In addition to dementia diagnosis for all participants, we also had access to two
322 composite scores designed by ADNI collaborators to reflect executive function and memory;
323 these scores have been demonstrated to be independently predictive of the transition from mild
324 cognitive impairment to a formal diagnosis of Alzheimer's disease (Gibbons et al. 2012, Gale et
325 al. 2013). By a two-way unbalanced ANOVA models investigating the effect of sex and memory
326 score on epigenetic age acceleration, neither sex (p=0.248), memory score (p=0.486), nor their
327 interaction (p=0.227) were associated with epigenetic age acceleration. In a similar model,

328 neither sex ($p=0.260$), executive function ($p=0.105$), or the interaction term of sex and executive
329 function ($p=0.153$) were associated with epigenetic age acceleration.

330

331 **Discussion**

332 In the present study, we found that tau related pathology in the CSF was
333 disproportionately elevated by APOE ϵ 4 genotype in females compared to males. However,
334 diagnosis and APOE genotype were independently associated with reduced memory scores,
335 hippocampal volume (corrected by intracranial volume) and reduced CSF amyloid beta which
336 was similar in males and females. Furthermore, there were main effects of sex as females had
337 lower CSF cytokines (IL-8, IL-16, IL-18) and CSF and plasma immunoglobulins (IgA, IgE,
338 respectively) but higher plasma CRP and tau related pathology compared to males, regardless of
339 diagnosis and APOE genotype. Interestingly, females had larger corrected hippocampal volume
340 and better memory scores which may contribute to their delayed diagnosis (Sundermann et al.,
341 2017). Finally, we found no differences in epigenetic age acceleration by dementia diagnosis or
342 sex in this cohort of samples with available whole blood EPIC DNAme data. In this ADNI
343 cohort, slightly more females presented with a diagnosis of AD compared to males, whereas
344 significantly more males presented with a diagnosis of MCI supporting the prevalence observed
345 in bigger populations (Winblad et al., 2016; Mielke et al., 2014). Previous work has
346 demonstrated sex differences in rates of AD and symptoms of AD (reviewed in Ferretti et al.,
347 2018; Mielke et al., 2014; Nebel et al., 2018), and the current study also suggests that biomarkers
348 of AD may be different between males and females between genotypes, and this should be
349 considered in future studies and researchers should be cautioned to use sex as a biological
350 variable in all analyses.

351

352 Females show greater tau neuropathology disproportionately affected by APOE genotype

353 In the present study, we found that females have significantly higher baseline tau and p-
354 tau levels in CSF than males and these are indicative of the formation of neurofibrillary tangles
355 and AD pathology (Blennow et al., 2015; Henriques et al., 2018). This is in agreement with a
356 recent ADNI study (Sundermann et al., 2018; but see an earlier ADNI study Holland et al.,
357 2013) and with animal models (Lewis et al., 2001). Intriguingly, we also found that levels of tau
358 and p-tau were disproportionately elevated with APOE ϵ 4 allele expression in females compared
359 to males. Previous studies indicate that females with the APOE ϵ 4 allele are at a greater risk for
360 developing AD than are males with this allele (Altmann et al., 2014), and sex differences in tau
361 and p-tau may be one underlying mechanism by which this occurs. In females (65-75 years of
362 age) one allele of ϵ 4 increases the risk of AD by 4-fold relative to males, indicating that genotype
363 may affect females differently (Neu et al., 2017). Levels of CSF tau are hypothesized to increase
364 after CSF amyloid beta declines and amyloid beta aggregates and deposits in the brain (Blennow
365 et al., 2015). However, in this study although we found sex differences in CSF tau and p-tau
366 levels, no significant differences were seen in CSF amyloid beta after controlling for age (see
367 below) indicating that the pathway may be different in females compared to males or that the
368 timeline of tau and amyloid beta deposition may not be consistent.

369 In this ADNI cohort, more females presented with a diagnosis of AD compared to males.
370 Although the ADNI cohort is relatively small, this result supports the prevalence observed in
371 bigger populations (Winblad et al., 2016). Together with the disproportionate effect of APOE
372 genotype on tau-related pathology it supports the idea that females have a higher burden of the
373 disease. On the other hand, more males presented with a diagnosis of MCI and this is in line with

374 the research that males are more likely to be diagnosed with MCI compared to females (Mielke
375 et al., 2014). Females progress faster from MCI to AD (Lin et al., 2015) and sex differences in
376 tau related pathology found in the current study may be the underlying mechanism for this
377 accelerated transition.

378

379 *Sex differences in hippocampal volume depend on correction for intracranial volume. Females*
380 *have better memory scores than males that may have been driven by verbal memory*

381 In the present study, we found that increasing APOE ϵ 4 alleles and AD diagnosis was
382 associated with reduced corrected hippocampal volume, memory and executive function scores
383 consistent with past literature (Apostolova et al., 2006; Buckner, 2004; Ewers et al., 2012; Jack
384 et al., 2000; Li et al., 2016; Mungas et al., 2010; Petersen et al., 2000; Pievani et al., 2011; Shi et
385 al., 2014). Surprisingly, although females have higher levels of tau and p-tau, they presented
386 with larger corrected hippocampal volume and better memory and executive function scores than
387 males, regardless of diagnosis and APOE genotype. Previous studies have suggested that there
388 are sex differences in hippocampal volume, favoring males, but the sex differences depend on
389 whether hippocampal volume is corrected for by intracranial volume (Tan et al., 2016), a finding
390 that is supported by the current study. In a number of studies, including the present study, males
391 have a larger hippocampus without correcting for intracranial volume (Cavedo et al., 2018; Jack
392 et al., 2015; Murphy et al., 1996; Ritchie et al., 2018; Sohn et al., 2018; Sundermann et al., 2018;
393 Tan et al., 2016). However after correcting for intracranial volume, either the sex difference
394 disappears (Cavedo et al., 2018; Ritchie et al., 2018; Tan et al., 2016) or females have larger
395 corrected hippocampal volume (this study; Jack et al., 2015; Murphy et al., 1996; Sohn et al.,
396 2018; Sundermann et al., 2018). Regardless of hippocampal volume, volume loss is greater in

397 aging females (Ardekani et al., 2016; Koran et al., 2017; Murphy et al., 1996) and in females
398 with one or two APOE ϵ 4 alleles (Fleisher et al., 2005). Although in the present study we did not
399 examine longitudinal data, we found that increasing APOE ϵ 4 alleles reduced corrected
400 hippocampal volume similarly in males and females. In contrast, when CN, MCI and AD
401 individuals were analysed separately in the ADNI database, APOE ϵ 4 was associated with a
402 smaller corrected hippocampal volume in CN males only, controlling for age and education
403 (Sundermann et al., 2018). In addition, also using the ADNI database, Koran et al. (2017) found
404 that females with low CSF amyloid beta had more hippocampal atrophy and faster decline in
405 memory and executive function than males and this sex difference was more pronounced in
406 APOE ϵ 4 carriers. Therefore, sex and APOE genotype can interact to affect corrected
407 hippocampal volume reduction with age in certain subgroups and across time (e.g., in CN or
408 individuals with low CSF amyloid beta). Differences in results between studies are likely due to
409 differences in statistical analyses (e.g., analysing diagnosis groups separately, partitioning the
410 data based on amyloid beta levels, and differences in covariates included) and/or whether
411 longitudinal data analyses are included.

412 We found that in addition to larger corrected hippocampal volume, females also had
413 better composite memory scores (but not executive function scores) than males, regardless of
414 diagnosis and APOE genotype. Previous studies have found that females have better verbal
415 memory in cognitively normal individuals (Jack et al., 2015), and in MCI and AD ADNI cohorts
416 compared to males (Sundermann et al., 2018, 2016). Here we used the ADNI memory score
417 developed by Crane et al. (2012) to detect abnormal memory including language, attention, and
418 logical memory so it is possible that verbal memory may be driving the sex difference favouring
419 females in the present study. In contrast, Buckley et al. (2018) found no sex differences using a

420 composite cognitive score that includes memory and executive function (Preclinical Alzheimer's
421 Cognitive Composite score with semantic processing, PACC5) using ADNI and two other
422 cohorts. In this study using the current ADNI cohort, males were slightly more educated than
423 females, and although we did not use education as a covariate, one would expect education levels
424 would have positive effects on memory, suggesting that education is not a factor for the observed
425 sex difference in memory. Altogether, we found that in females tau pathology was increased but
426 memory scores, which included verbal memory, were higher and corrected hippocampal volume
427 were larger compared to males suggesting females have a reserve against brain damage that
428 delays either the onset of cognitive decline (Stern, 2002) or diagnosis (Sundermann et al., 2017).
429 However, once cognitive decline begins, females show higher rates of declines compared to
430 males (this was observed by Buckley et al., 2018; Holland et al., 2013; Hua et al., 2010 using the
431 ADNI database) perhaps because the underlying pathology is elevated in females.

432

433 *AD affects amyloid beta similarly in both sexes*

434 We found that AD diagnosis was associated with lower CSF amyloid beta, as expected,
435 and this was irrespective of sex, which indicates greater amyloid deposition with AD (Henriques
436 et al., 2018). These findings are consistent with data from studies in AD patients (Buckley et al.,
437 2018) and in cognitively normal individuals (Jack et al., 2015). Other studies have found using
438 PET that males have higher amyloid beta levels or lower amyloid beta burden compared to
439 females dependent on APOE genotype (Sundermann et al., 2018) or in cognitively normal adults
440 in the anterior cingulate (Cavedo et al., 2018). In this study, we used CSF amyloid beta data
441 which detects abnormal amyloid deposition earlier than amyloid beta by PET (reviewed in
442 Blennow et al., 2015). Thus, taken together, sex differences in amyloid beta may be detected in

443 specific brain regions and later in the disease, although more research is needed investigating sex
444 differences in AD biomarkers.

445

446 *Females have higher CRP levels but lower cytokine and immunoglobulin levels compared to*
447 *males*

448 In this study, we investigated whether sex interacted with APOE genotype or dementia
449 diagnosis to influence inflammatory, neurotrophic and neuroplasticity markers. We found that
450 plasma CRP, a widely used inflammatory and cardiovascular marker (Koenig et al., 1999; Ridker
451 et al., 1998), was affected by sex and APOE genotype. Females, regardless of diagnosis or
452 APOE genotype, had significantly higher plasma CRP relative to males, consistent with findings
453 in healthy individuals (Khera et al., 2005). Higher levels of peripheral CRP may suggest higher
454 inflammation in females, which is associated with an increased risk in all-cause dementia
455 (Koyama et al., 2013). In contrast, APOE ϵ 4 genotype decreased circulating CRP levels,
456 consistent with previous research in large population studies (Hubacek et al., 2010; Yun et al.,
457 2015). Recent meta-analyses, without regard to sex, did not find differences in peripheral levels
458 of CRP in AD compared to control patients (Gong et al., 2016; Ng et al., 2018). However, in
459 patients with mild and moderate dementia only, CRP levels were lower compared to the healthy
460 control group (Gong et al., 2016). To our knowledge, no other study has examined sex
461 differences in CRP in relation to AD.

462 We also found that CSF IL-16 was affected by sex and APOE genotype. CSF IL-16
463 levels were lower in females with no APOE ϵ 4 alleles compared to males, but with increasing
464 number of ϵ 4 alleles, no sex differences were detected. IL-16 has been implicated in AD (Rosa et
465 al., 2006) and IL-16 levels decrease with disease severity (analysis without regard to sex; Motta

466 et al., 2007). In this ADNI cohort, IL-16 levels were not affected by diagnosis but our results
467 suggest that APOE genotype can modulate levels in a sex-dependent way. We also found
468 biomarkers that were affected by sex but not diagnosis or APOE genotype for example, females
469 had lower CSF levels of ICAM1 compared to males, but there was no influence of APOE
470 genotype or diagnosis. Consistent with our findings, ICAM1 serum levels were lower in healthy
471 females compared to males (Ponthieux et al., 2003). ICAM1 is a type of adhesion molecule
472 associated with microvascular endothelial activation (Zenaro et al., 2017) and plasma ICAM1
473 levels (but not CSF levels; Nielsen et al 2007) were higher in patients with AD (Huang et al
474 2015; Nielsen et al 2007; Rentzos et al 2004). However, it is intriguing that females have lower
475 CSF levels of cytokines (IL-8, IL-16, IL-18), and immunoglobulins (IgE and IgA) but higher tau
476 pathology compared to males. Neuroinflammation is associated with AD but it can have both
477 beneficial and detrimental roles (Walters et al., 2016). Increased expression of pro-inflammatory
478 cytokines contributes to neuronal loss, while anti-inflammatory effects contribute to amyloid
479 beta clearance (Heneka et al., 2015). In AD mouse models, some pro-inflammatory mechanisms
480 reduced plaque pathology, while anti-inflammatory cytokines increased amyloid beta deposition
481 (Chakrabarty et al., 2012, 2011, 2010a, 2010b; Ghosh et al., 2013; Shaftel et al., 2007). It has
482 been suggested that there are beneficial pro-inflammatory mechanisms and detrimental anti-
483 inflammatory mechanisms in AD (Heneka et al., 2015). It is possible that males and females
484 have varying levels of beneficial vs detrimental immune responses which can affect how the
485 disease progresses in each of the sexes but it is also important to remember that CSF levels may
486 not match levels in different regions of the brain.

487

488 Sex, AD and biochemical markers do not affect blood epigenetic age acceleration

489 We did not observe an association between either sex or diagnosis and epigenetic age
490 acceleration or intrinsic epigenetic age acceleration. To our knowledge, no other study has
491 similarly probed epigenetic age acceleration in peripheral tissue in the presence of AD, or
492 whether epigenetic age acceleration in AD is associated with sex.

493 This study was partially undertaken to investigate whether epigenetic age acceleration
494 that has been associated with the AD brain is reflected in peripheral tissues. Levine et al. have
495 previously demonstrated increased epigenetic age acceleration in AD, however Levine's study
496 was conducted on post-mortem prefrontal cortex tissue, and did not explicitly investigate the role
497 of sex in epigenetic age acceleration (Levine et al., 2015). While brain-blood methylation
498 profiles are reasonably correlated ($r=0.86$) (Braun et al., 2019), DNA methylation profiles of
499 peripheral tissues are imperfect representatives of the brain, and do not recapitulate all epigenetic
500 alterations with high fidelity. Thus, our findings do not contradict the finding of increased
501 epigenetic age acceleration in the presence of AD in the prefrontal cortex, but suggest that
502 accelerated epigenetic aging in AD is not a pan-tissue phenomenon. Our finding of a lack of
503 significant association between AD, biological sex, and epigenetic age acceleration in whole
504 blood DNA methylation profiles could suggest a tissue-specific dysregulation of an epigenetic
505 maintenance system, in which the brain epigenome is most strongly affected by AD (Levine et
506 al., 2015). The phenotype of patients affected by AD and global gene expression patterns of the
507 APOE protein, with high expression in brain, and low expression in whole blood (GTEx Project,
508 2018) further support this hypothesis.

509 Intriguingly, epigenetic age was observed to be lower on average than chronological age
510 (see Table 5). Horvath's epigenetic clock was trained on DNAm data from older versions of the
511 Illumina DNAm arrays with more limited genomic coverage; 19 of the CpG probes required to

512 calculate epigenetic age via this method do not exist on the EPIC array. Two previous studies
513 investigated the application of Horvath's epigenetic clock to EPIC data with conflicting results
514 (Dhingra et al., 2019; McEwen et al., 2018), the largest issue being chronic underestimation of
515 epigenetic age due to the positive linear regression coefficients associated with the missing
516 probes(Dhingra et al., 2019). Both imputing and removing the missing probes from the array
517 resulted in a chronic underprediction of epigenetic age with Horvath's clock, suggesting that this
518 is likely an artefact of the array platform and probe-set rather than the method chosen to deal
519 with missing values, although it is possible that an adjustment factor could be devised to more
520 accurately apply Horvath's clock to EPIC data. In future explorations of epigenetic age with
521 EPIC DNAme array data this should be considered, as there are other epigenetic age predictors
522 available that have been trained on EPIC data such as the PhenoAge and GrimAge clocks,
523 although these tools have limitations as well; for example, both PhenoAge and GrimAge were
524 trained only on blood DNAme data, as compared to the original pan-tissue epigenetic clock, and
525 therefore may have limited applicability and relevance in other tissues (Levine et al., 2018; Lu et
526 al., 2019).

527

528 **Limitations**

529 The ADNI cohort is not ethnically or socioeconomically diverse, being mostly composed
530 of white (only 12 individuals were not-white) and highly educated individuals (average 15.69
531 years of education). As incidence, prevalence, and age of onset of AD varies by ethnicity
532 (Hispanics, Fitten et al., 2014; Mayeda et al., 2016; African-Americans, Steenland et al., 2016)
533 and education (Sharp and Gatz, 2011), our conclusions may not apply to more ethnically and
534 socially diverse populations. In addition to sex, it is possible the underlying mechanisms of AD

535 are different depending on ethnicity. Finally, the ADNI biomarker data set has a low sample size
536 (279 total), especially when taking into account diagnosis, sex and APOE genotype. Small
537 sample size is also a limitation of the epigenetic analyses presented. Even in the larger 640-
538 participant cohort, only 37 participants (5.78%) had an AD diagnosis, so statistical analyses were
539 underpowered to detect subtle differences by diagnosis group. Additionally other pathologies in
540 these participants, such as cancer, cardiovascular disease, smoking status, or obesity may have
541 influenced AD neuropathology, biomarkers and epigenomes and limited our interpretations.

542

543 **Conclusion**

544 As expected, more females presented with a diagnosis of AD whereas more males
545 presented with MCI diagnosis compared to the opposite sex. AD biomarkers (CSF tau and p-tau
546 but not amyloid beta) were disproportionately affected by APOE genotype in females compared
547 to males supporting the idea that females share a higher burden of the disease. Interestingly,
548 although females in this cohort had elevated AD biomarkers, they also had larger corrected
549 hippocampal volume and higher memory function scores compared to males, regardless of
550 APOE genotype and dementia diagnosis. Therefore, it is possible that females may have a
551 reserve that protects the brain from damage to delay cognitive decline or delay diagnosis.
552 Finally, we found that females had lower cytokine and immunoglobulin levels but higher CRP
553 levels compared to males. Together our work suggests that the underlying physiology of
554 aging and AD may be sex-specific.

555

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584

585 **Figure captions**

586 **Figure 1.** A. CSF tau (pg/ml), B. CSF p-tau (pg/ml), C. CSF IL-16 (pg/ml), D. ADNI memory z-
587 scores, E. corrected hippocampal volume (hippocampal volume/intracranial volume), F. ADNI
588 executive function z-scores, G. CSF amyloid beta (pg/ml), and H. CSF C-reactive protein (CRP;
589 µg/ml) in ADNI participants by sex and number of APOEε4 alleles (0, 1, 2 alleles).

590

591 **Figure 2.** A. ADNI memory z-scores, B. corrected hippocampal volume (hippocampal volume/
592 intracranial volume), C. CSF tau (pg/ml), D. CSF p-tau (pg/ml), E. CSF IL-16 (pg/ml), F. CSF
593 IL-8 (pg/ml), G. CSF IgA (mg/ml), H. CSF Intercellular adhesion molecule (ICAM1; ng/ml), I.
594 ADNI executive function z-scores, J. CSF amyloid beta (pg/ml), K. plasma C-reactive protein
595 (CRP; µg/ml), and L. plasma cortisol (ng/ml) in ADNI participants by sex and diagnosis (CN,
596 EMCI, LMCI, AD). CN, cognitively normal; EMCI, early mild cognitive impairment; LMCI,
597 late mild cognitive impairment; AD, Alzheimer's disease.

598

599 **Figure 3.** Universal epigenetic age acceleration does not differ statistically significantly by
600 participant sex or diagnosis (CN, EMCI, LMCI, AD) in this ADNI cohort. CN, cognitively
601 normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD,
602 Alzheimer's disease.

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1002

Table 1. Demographic and clinical information for all participants and subdivided by sex. Biomarkers for AD are from cerebrospinal fluid. P-values after adjusting for age are presented here for easier comparison and are taken from the linear model of sex and diagnosis (see Table 3 for details).

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		Sex		P-value	P-value (adjusted for age)
Total	Female	Male			
	No. 1,460	No. 630	No. 830		
Age					
Mean (SD)	74.13 (± 7.25)	73.15 (± 7.28)	74.87 (± 7.14)	< 0.0001	
Education (years)					
Mean (SD)	15.83 (± 2.88)	15.15 (± 2.79)	16.34 (± 2.85)	< 0.0001	
Ethnicity					
White	1,352 (92.60%)	573 (90.95%)	779 (93.86%)	0.043	
Not white	108 (7.40%)	57 (9.05%)	51 (6.14%)		
Baseline diagnosis					
CN	341 (23.4%)	168 (26.7%)	173 (20.8%)	0.013	
EMCI	257 (17.6%)	108 (17.1%)	149 (18.0%)		
LMCI	533 (36.5%)	205 (32.5%)	328 (39.5%)		
AD	329 (22.5%)	149 (23.7%)	180 (21.7%)		
APOEϵ4 allele number					
0	702 (48.08%)	300 (47.62%)	402 (48.43%)	0.8	
1	574 (39.32%)	252 (40.00%)	322 (38.80%)		
2	170 (11.64%)	70 (11.11%)	100 (12.05%)		
Missing	14 (0.96%)	8 (1.27%)	6 (0.72%)		
Volume of hippocampus					
Mean (SD)	6659.47 (± 1176.42)	6446.71 (± 1169.97)	6822.86 (± 1155.87)	< 0.0001	
Missing	226 (15.48%)	94 (14.92%)	132 (15.90%)		
Volume of hippocampus (corrected)					
Mean (SD)	0.00436 (± 0.00080)	0.00454 (± 0.00082)	0.00423 (± 0.00076)	< 0.0001	< 0.0001
Missing	226 (15.48%)	94 (14.92%)	132 (15.90%)		
Amyloid Beta					
Mean (SD)	830.97 (± 358.04)	856.41 (± 346.87)	812.44 (± 365.16)	0.016	0.38
Missing	513 (35.14%)	231 (36.67%)	282 (33.98%)		
Tau					
Mean (SD)	294.38 (± 137.27)	314.56 (± 152.70)	279.70 (± 122.91)	0.002	< 0.0001
Missing	513 (35.14%)	231 (36.67%)	282 (33.98%)		
PTau					
Mean (SD)	28.89 (± 15.31)	30.87 (± 16.95)	27.44 (± 13.83)	0.007	< 0.0001
Missing	513 (35.14%)	231 (36.67%)	282 (33.98%)		
Executive Function (ADNI_EF)					
Mean (SD)	0.02 (± 0.96)	0.06 (± 0.97)	-0.00 (± 0.95)	0.20	< 0.0001
Missing	311 (21.30%)	145 (23.02%)	166 (20.00%)		
Memory (ADNI_MEM)					
Mean (SD)	0.10 (± 0.87)	0.21 (± 0.94)	0.02 (± 0.80)	0.0006	< 0.0001
Missing	310 (21.23%)	145 (23.02%)	165 (19.88%)		

P-values are from Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. Missing refers to number of individuals and the percent of the total cohort that had missing data for that variable

Table 2. Demographic and clinical information for subset of ADNI data subdivided by sex. A. Participants with measured biomarkers in cerebrospinal fluid (CSF), B. Participants with available whole blood Illumina HumanMethylationEPIC DNA methylation data, C. Participants with matched Illumina HumanMethylationEPIC DNA methylation array data and measured CSF biomarkers. In all three subdata sets, females were significantly younger and had fewer years of education than males. In data set A (but not B and C), more females (24.0 % compared to 21.8%) were diagnosed with AD, more females were cognitively normal (26.5% compared to 22.9%) and fewer females were diagnosed with late MCI compared to males (49.5% compared to 55.3%). In data set A, females had lower CSF cortisol, interleukin-3, interleukin 8, interleukin-16, immunoglobulin A, and intercellular adhesion molecule compared to males. Empty cells indicate data not available.

	A				B				C			
	Sex				Sex				Sex			
	Total No. 279	Female No. 109	Male No. 170	P-value	Total No. 640	Female No. 284	Male No. 356	P-value	Total No. 533	Female No. 243	Male No. 290	P-value
Age												
Mean (SD)	75.15 (\pm 6.86)	73.75 (\pm 6.69)	76.04 (\pm 6.83)	0.007	75.63 (\pm 7.68)	74.78 (\pm 8.03)	76.31 (\pm 7.32)	<0.0001	75.01 (\pm 7.61)	74.31 (\pm 8.10)	75.61 (\pm 7.11)	0.0019
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Education (years)	Mean (SD)	12.99 (\pm 2.70)	16.21 (\pm 2.70)	<0.0001	15.53 (\pm 2.59)	16.75 (\pm 2.68)	<0.0001	16.24 (\pm 2.64)	15.57 (\pm 2.49)	16.83 (\pm 2.64)	<0.0001	
Ethnicity												
White	267 (95.70%)	103 (94.50%)	164 (96.47%)	0.55	627 (97.97%)	279 (98.23 %)	348 (97.75%)	0.78	521 (97.75 %)	238 (97.94 %)	283 (97.94 %)	0.99
Not White [†]	12 (4.30%)	6 (5.50%)	6 (3.53%)		13 (2.03%)	5 (1.76%)	8 (2.25%)		12 (2.25 %)	5 (2.06 %)	7 (2.41 %)	
Baseline diagnosis												
CN	74 (26.5%)	35 (32.1%)	39 (22.9%)	0.051	217 (33.9%)	109 (38.38%)	108 (30.34%)	0.11	171 (32.08 %)	88 (36.21 %)	83 (28.62 %)	0.19
EMCI	n/a	n/a	n/a		186 (29.06%)	83 (29.23%)	103 (28.93%)		173 (32.46 %)	79 (32.51 %)	94 (32.41 %)	
LMCI	138 (49.5%)	44 (40.4%)	94 (55.3%)		200 (31.25%)	78 (27.46%)	122 (34.27%)		155 (29.08 %)	94 (38.68 %)	92 (31.72 %)	
AD	67 (24.0%)	30 (27.5%)	37 (21.8%)		37 (5.78%)	14 (4.23 %)	23 (6.46%)		34 (6.38 %)	13 (5.35 %)	21 (7.24 %)	
APOEϵ4 allele number												
0	134 (48.03%)	51 (46.79%)	83 (48.82%)	0.78	369 (57.66 %)	169 (59.51%)	200 (56.18%)	0.37	313 (58.72 %)	146 (60.08 %)	167 (57.59 %)	0.45
1	109 (39.07%)	42 (38.53%)	67 (39.41%)		220 (34.38%)	97 (34.15%)	123 (34.55%)		173 (32.46%)	80 (32.92 %)	93 (32.07 %)	
2	36 (12.90%)	16 (14.68%)	20 (11.76%)		51 (7.97%)	18 (6.34%)	33 (9.27%)		47 (8.82%)	17 (7.00%)	30 (10.34 %)	
Cortisol (ng/mL)												
Mean (SD)	16.05 (\pm 6.04)	14.92 (\pm 6.01)	16.78 (\pm 5.96)	0.008								
C reactive protein (ug/mL)												
Mean (SD)	-2.83 (\pm 0.56)	-2.77 (\pm 0.64)	-2.87 (\pm 0.51)	0.23								
CD40 antigen (ng/mL)												
Mean (SD)	-0.65 (\pm 0.12)	-0.66 (\pm 0.10)	-0.64 (\pm 0.14)	0.12								
Interleukin 16 (pg/mL)												
Mean (SD)	0.91 (\pm 0.18)	0.87 (\pm 0.17)	0.94 (\pm 0.19)	0.004								
Interleukin 3 (ng/mL)												
Mean (SD)	-2.22 (\pm 0.32)	-2.28 (\pm 0.29)	-2.17 (\pm 0.34)	0.001								
Interleukin 6 receptor (ng/mL)												
Mean (SD)	-0.01 (\pm 0.15)	-0.02 (\pm 0.14)	-0.00 (\pm 0.15)	0.30								
Interleukin 8 (pg/mL)												
Mean (SD)	1.68 (\pm 0.15)	1.64 (\pm 0.11)	1.70 (\pm 0.16)	0.001								
Intercellular adhesion molecule (ng/mL)												
Mean (SD)	0.96 (\pm 0.44)	0.83 (\pm 0.33)	1.04 (\pm 0.48)	0.0001								
Immunoglobulin A (mg/mL)												
Mean (SD)	-2.54 (\pm 0.31)	-2.68 (\pm 0.26)	-2.45 (\pm 0.31)	<0.0001								
Executive Function Score												
Mean (SD)					0.36 (\pm 0.98)	0.38 (\pm 1.01)	0.34 (\pm 0.95)	0.17				
Memory Score												
Mean (SD)					0.40 (\pm 0.92)	0.57 (\pm 1.01)	0.26 (\pm 0.82)	<0.0001				
Amyloid Beta												
Mean (SD)									1040.98 (\pm 454.72)	1055.50 (\pm 449.23)	1028.35 (\pm 459.36)	0.18
Tau												
Mean (SD)									289.80 (\pm 124.68)	300.90 (\pm 139.07)	280.13 (\pm 109.82)	0.072
PTau												
Mean (SD)									27.47 (\pm 13.65)	28.25 (\pm 15.08)	26.78 (\pm 12.24)	0.36

P-values are from Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. [†]Includes self-reported Black, Asian, American Indian/Alaskan, and >1 ethnicity.

Table 3. Linear regression results for models with sex and APOE status. Only shown are the models with significant associations. All model summaries are available in Supplementary Table S1.

Table 3. Continued

C Reactive Protein ug/ml				Interleukin 16 pg/ml				Interleukin 8.IL 8.pg m L				Immunoglobulin A mg/ml			Intercellular Adhesion Molecule 1 ng/ml		
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p		
(Intercept)	-3.05	-3.79 – -2.32		0.35	0.10 – 0.59		1.38	1.18 – 1.57		-2.82	-3.22 – -2.43		-0.19	-0.75 – 0.36			
AGE (years)	0.01	-0.00 – 0.02		0.01	0.00 – 0.01		0	0.00 – 0.01		0	-0.00 – 0.01		0.01	0.01 – 0.02			
Male (ref = Female)	-0.12	-0.26 – -0.01	0.15	0.12	0.06 – 0.18		0.1	0.05 – 0.15	0.01	0.21	0.14 – 0.29	<0.0001	0.18	0.07 – 0.28	0.002		
APOE status (ref = 0 alleles)			0.007						0.33				0.27		0.31		
1 allele	-0.19	-0.33 – -0.05		0.08	0.01 – 0.16		0.04	-0.02 – 0.10		0.02	-0.05 – 0.10		0.09	-0.01 – 0.20			
2 alleles	-0.31	-0.52 – -0.10		0.06	-0.04 – 0.16		0.01	-0.07 – 0.09		-0.09	-0.20 – 0.02		0.02	-0.13 – 0.18			
Interaction term						0.02											
Male:1 allele				-0.13	-0.22 – -0.03												
Male:2 alleles				-0.15	-0.28 – -0.02												
Observations		279		279				279		279			279		279		
R ² / adjusted R ²	0.058 / 0.045			0.117 / 0.098			0.092 / 0.072			0.135 / 0.122			0.107 / 0.094			0.279	

Table 4. Linear regression results for models with sex and baseline diagnosis. Only shown are the models with significant associations. P-values are for overall tests and are FDR-adjusted. All model summaries are available in Supplementary Table S2.

ADNI MEM				ADNI EF				ABETA				Hippocampus/Intracranial volume				TAU				PTAU	
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p
(Intercept)	1.79	1.45 – 2.13		2.26	1.80 – 2.73		1161.57	944.04 – 1379.10		0.00747	0.00710 – 0.00785		154.16	70.57 – 237.75		15.72	6.36 – 25.09				
AGE (years)	-0.01	-0.01 – -0.00		-0.02	-0.03 – -0.01		-1.64	-4.52 – 1.24		-0.00003	-0.00004 – -0.00003		1.25	0.15 – 2.36		0.1	-0.02 – 0.23				
Male (ref = Female)	-0.16	-0.23 – -0.09	<0.0001	-0.04	-0.13 – 0.05	0.53	-26.62	-69.46 – 16.22	0.38	-0.00022	-0.00029 – -0.00015	<0.0001	-42.59	-59.05 – -26.13	<0.0001	-4.22	-6.06 – -2.38	<0.0001			
Diagnosis (ref = CN)			<0.0001						<0.0001			<0.0001			<0.0001			<0.0001		<0.0001	
EMCI	-0.5	-0.61 – -0.39		-0.42	-0.56 – -0.27		-85.2	-148.82 – -21.59		-0.00016	-0.00027 – -0.00005		37.85	13.41 – 62.30		4.22	1.48 – 6.96				
LMCI	-1.08	-1.16 – -1.00		-0.79	-0.90 – -0.67		-256.85	-315.81 – -197.89		-0.00073	-0.00083 – -0.00064		93.34	70.69 – 116.00		10.58	8.05 – 13.12				
AD	-1.84	-1.94 – -1.75		-1.63	-1.76 – -1.50		-390.48	-453.59 – -327.37		-0.00106	-0.00116 – -0.00096		143.6	119.35 – 167.8		15.81	13.10 – 18.53				
Observations	1150			1149			947			1234			947			947			947		

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Table 4. Continued

Interleukin 16 pg/ml				Interleukin 8 pg/ml				Immunoglobulin A mg/ml				Intercellular Adhesion Molecule 1 ng/ml			
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p
(Intercept)	0.42	0.18 – 0.65		1.4	1.20 – 1.59		-2.9	-3.29 – -2.50		-0.22	-0.77 – 0.33				
AGE (years)	0.01	0.00 – 0.01		0	0.00 – 0.01		0	-0.00 – 0.01		0.01	0.01 – 0.02				
Male (ref = Female)	0.05	0.01 – 0.10	0.06	0.05	0.01 – 0.09	0.02	0.21	0.14 – 0.29	<0.0001	0.17	0.06 – 0.27	0.006			
Diagnosis (ref = CN)			0.64			0.96			0.98			0.67			
EMCI															
LMCI	0.01	-0.04 – 0.06		0.01	-0.03 – 0.05		0	-0.08 – 0.09		0.06	-0.06 – 0.18				
AD	-0.03	-0.08 – -0.03		0.01	-0.04 – -0.06		-0.01	-0.11 – -0.09		0.02	-0.12 – -0.16				
Observations	279			279			279			279			279		
R ² / adjusted R ²	0.089 / 0.075			0.059 / 0.045			0.123 / 0.111			0.101 / 0.088					

Table 5. Results of epigenetic age and epigenetic age acceleration calculation for all DNAm analyses, for both the larger DNAm cohort and the subset of samples with matched CSF biomarker data.

	DNAm Cohort				DNAm & CSF Biomarker Data Cohort					
	Total No. 640	Sex			P-value	Total No. 533	Sex			P-value
		Female No. 284	Male No. 356				Female No. 243	Male No. 290		
Age										
Mean (SD)	75.63 (± 7.68)	74.78 (± 8.03)	76.31 (± 7.32)		<0.0001	75.01 (± 7.61)	74.31 (± 8.10)	75.61 (± 7.11)	0.0019	
Epigenetic Age (years)										
Mean (SD)	69.92 (± 8.06)	67.45 (± 8.15)	70.11 (± 7.79)		<0.0001	68.47 (± 8.17)	67.05 (± 8.33)	69.72 (± 7.82)	<0.0001	
Epigenetic Age Acceleration (years)										
Mean (SD)	0.025 (± 4.22)	-0.14 (± 4.16)	0.16 (± 4.26)		0.1	0.027 (± 4.30)	-0.18 (± 4.23)	0.20 (4.35)	0.057	
Intrinsic Age Acceleration (years)										
Mean (SD)	0.026 (± 4.11)	-0.19 (± 4.06)	0.20 (± 4.15)		0.019	0.020 (± 4.18)	-0.25 (± 4.14)	0.26 (± 4.21)	0.021	

P-values are from Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables

Table 6. Linear model for assessment of relationship of biochemical concentrations and APOE genotype on universal epigenetic age acceleration. Intrinsic epigenetic age acceleration linear model not shown.

Age Acceleration & CSF Biomarkers			
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>
(Intercept)	-1.18	-2.80 – 0.45	0.517
Male (ref = Female)	0.65	-0.61 – 1.37	0.448
Diagnosis (ref = CN)			
EMCI	0.77	-0.12 – 1.65	0.09
LMCI	0.47	-0.51 – 1.45	0.569
AD	0.54	-1.10 – 2.19	0.738
APOE status (ref = 0 alleles)			
1 allele	-0.031	-0.09 – 0.84	0.945
2 alleles	-0.3	-1.75 – 1.14	0.813
CSF Amyloid Beta	0.00018	-0.00083 – 0.0011	0.813
CSF Tau	0.0078	-0.0077 – 0.023	0.569
CSF PTau	-0.072	-0.22 – 0.072	0.569
Observations			533
R ² / adjusted R ²	0.0143/-0.00262		

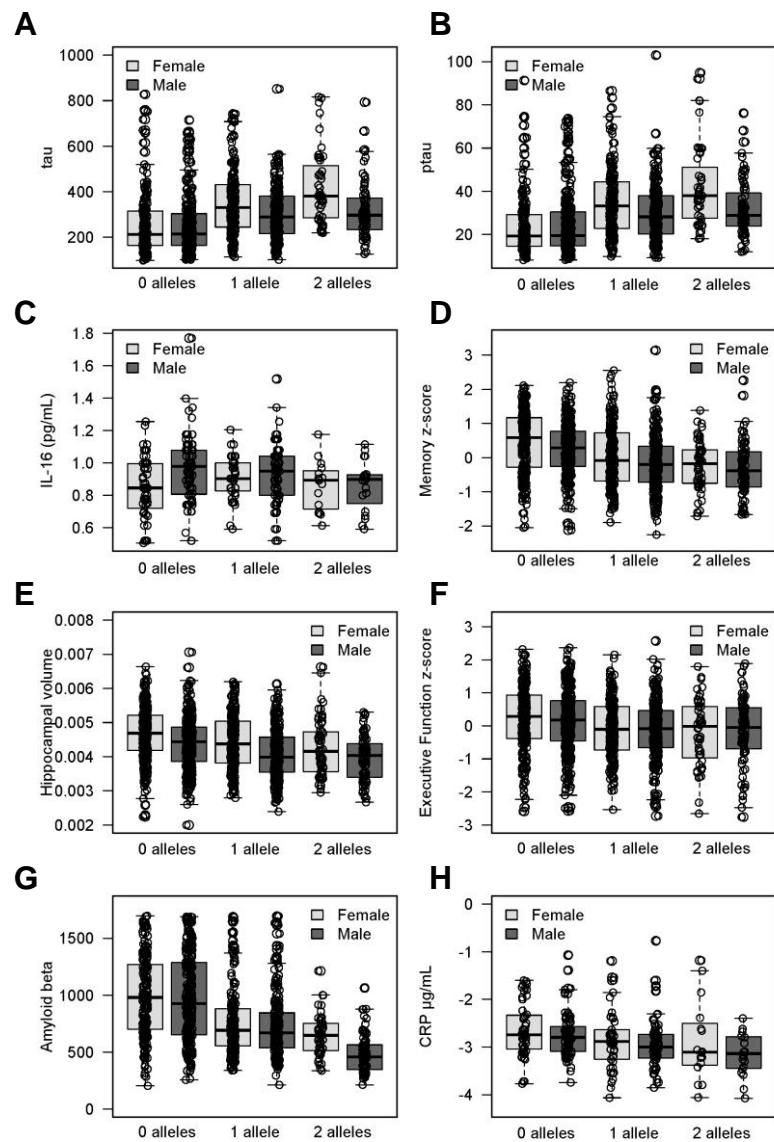
Figure 1

Figure 2

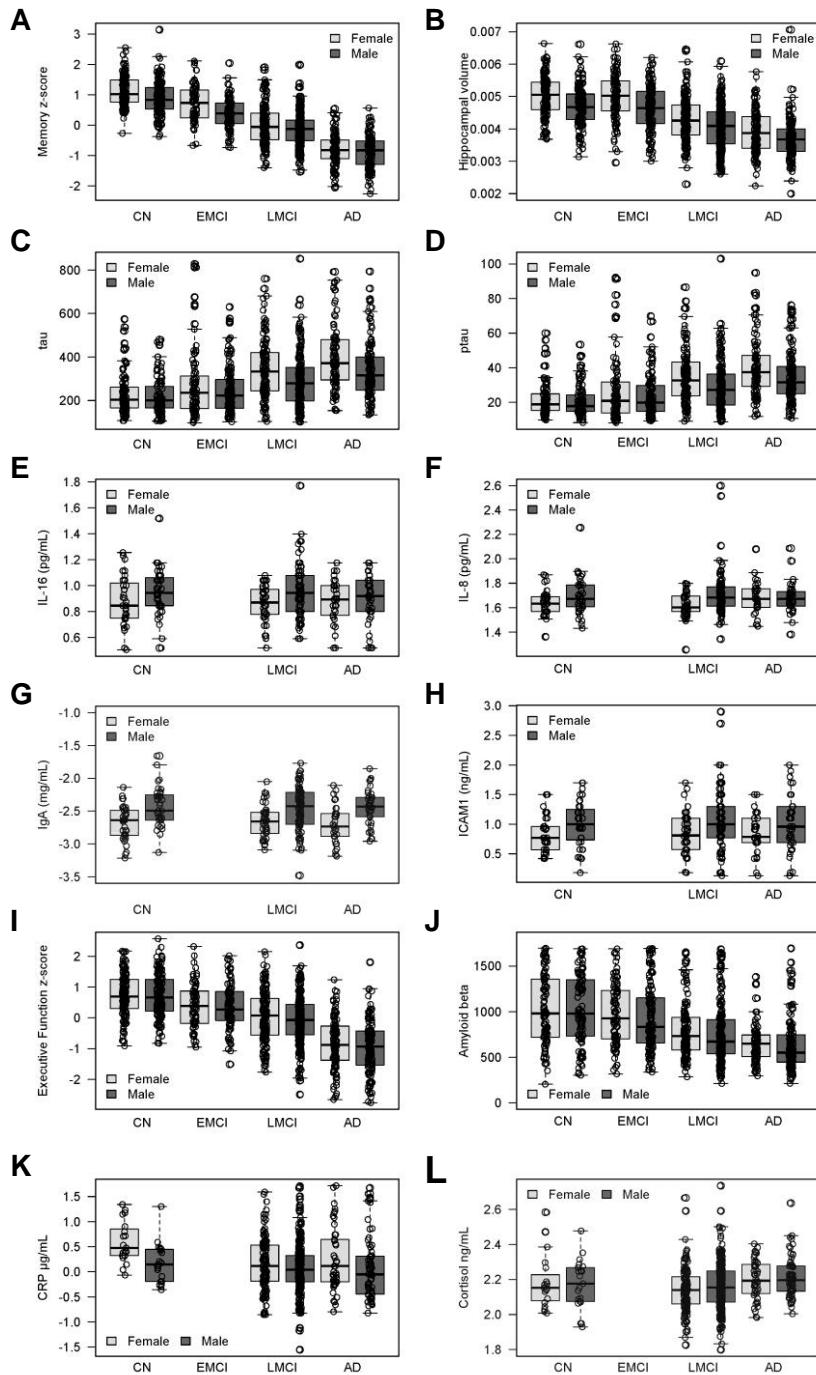
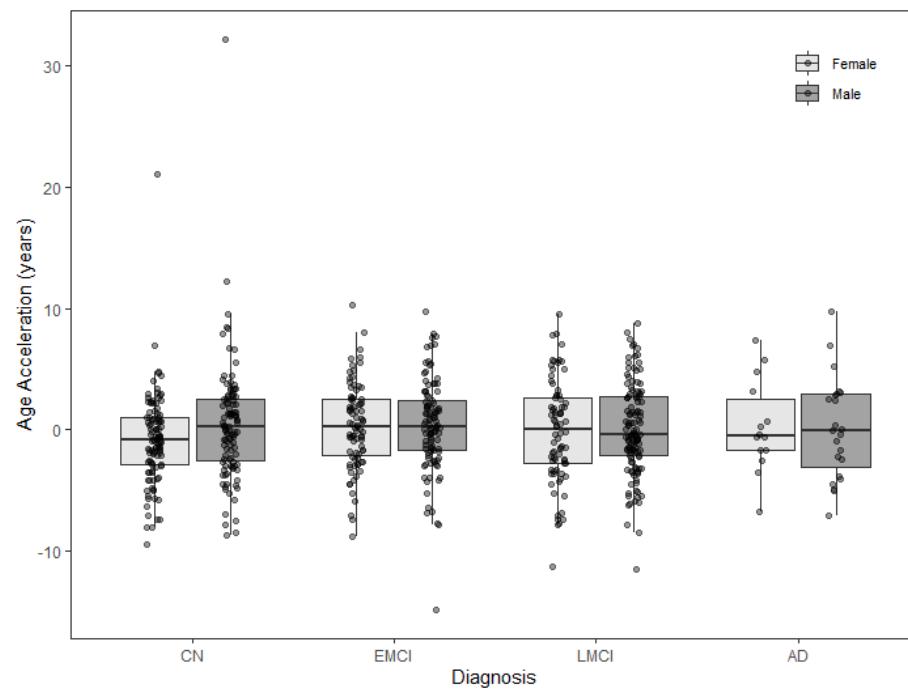


Figure 3



Supplemental File

Sex and APOE genotype influence AD neuropathology but not epigenetic age across diagnosis

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Table S2. Linear regression results for all variables investigated by sex and baseline diagnosis. Markers in CSF

Table S2 (continued). Linear regression results for all variables investigated by sex and baseline diagnosis. Markers in CSF

Table S2 (continued). Linear regression results for all variables investigated by sex and baseline diagnosis. MARKERS IN CSF																									
CD 40 antigen ng/ml				Interleukin 16 pg/ml				Interleukin 3 ng/ml				Interleukin 6.receptor ng/ml				Interleukin 8 pg/ml				Immunoglobulin A mg/ml			Intercellular Adhesion Molecule ng/ml		
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	
(Intercept)	-1.11	-1.27 – -0.96		0.42	0.18 – 0.65		-3	-3.42 – -2.59		-0.26	-0.45 – -0.07		1.4	1.20 – 1.59		-2.9	-3.29 – -2.50		-0.22	-0.7 – -0.33					
AGE (years)	0.01	0.00 – 0.01		0.01	0.00 – 0.01		0.01	0.00 – 0.02		0	0.00 – 0.01		0	0.00 – 0.01		0	-0.00 – 0.01		0.01	0.01 – 0.02					
Male (ref = Female)	0.01	-0.02 – 0.03	0.77	0.05	0.01 – 0.10	0.06	0.08	0.01 – 0.16	0.11	0.01	-0.02 – 0.05	0.67	0.05	0.01 – 0.09	0.02	0.21	0.14 – 0.29	<0.0001	0.17	0.06 – 0.27	0.006				
Diagnosis (ref = CN)				0.18			0.64			0.64			0.64			0.96			0.98			0.67			
EMCI																									
LMCI	0.01	-0.03 – 0.04		0.01	-0.04 – 0.06		-0.04	-0.13 – 0.05		0.01	-0.03 – 0.05		0.01	-0.03 – 0.05		0	-0.08 – 0.09		0.06	-0.06 – 0.18					
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Observations		279			279			279			279			279			279			279			279		
R ² / adjusted R ²	0.138 / 0.125				0.089 / 0.075			0.077 / 0.063			0.031 / 0.017			0.059 / 0.045			0.123 / 0.111			0.101 / 0.08					

Table S3. Linear regression results for all plasma variables investigated by sex and APOE genotype

Interleukin 18 pg/ml				Cortisol Cortisol ng/ml				C Reactive Protein ug/ml				Intercellular Adhesion Molecule ng/ml				Immunoglobulin E ng/ml				Interleukin 8 pg/ml					
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	
(Intercept)	2.41	2.25 – 2.57		2.04	1.92 – 2.16		0.06	-0.39 – 0.52		1.91	1.78 – 2.04		1.66	1.18 – 2.14		0.79	0.62 – 0.96								
AGE (years)	0	-0.00 – 0.00		0	-0.00 – 0.00		0	-0.00 – 0.01		0	-0.00 – 0.00		0	-0.01 – 0.01		0	0.00 – 0.01								
Male (ref = Female)	0.06	0.03 – 0.09	0.002	0.01	-0.01 – 0.04	0.54	-0.15	-0.25 – -0.06	0.009	-0.04	-0.06 – -0.01	0.07	0.25	0.15 – 0.34	<0.0001	-0.01	-0.04 – 0.03	0.82							
APOE status (ref = 0 alleles)		0.29			0.46				<0.0001			0.89				0.49								0.41	
1 allele	-0.03	-0.07 – -0.00		0.01	-0.01 – -0.04		-0.28	-0.37 – -0.18		0.01	-0.02 – -0.04		0.03	-0.06 – -0.13		-0.03	-0.07 – 0.00								
2 alleles	-0.04	-0.09 – -0.01		0.03	-0.00 – -0.07		-0.36	-0.50 – -0.23		0	-0.04 – -0.04		-0.1	-0.25 – -0.04		-0.03	-0.09 – -0.02								

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R² / adjusted R² 0.038 / 0.031 0.014 / 0.007 0.105 / 0.098 0.019 / 0.012 0.056 / 0.048 0.027 / 0.019 527 527 527

Table S3 (continued). Linear regression results for all plasma variables investigated by sex and APOE genotype

CD 40 antigen ng/ml				Interleukin 16.IL 16.pg m				Interleukin 3 ng/ml				Interleukin 6 receptor ng/ml				Immunoglobulin A mg/ml						
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p				
(Intercept)	-0.58	-0.68 – -0.47		2.32	2.18 – 2.47		-1.71	-1.98 – -1.45		1.42	1.30 – 1.55		0.48	0.28 – 0.69								
AGE (years)	0.01	0.00 – 0.01		0	0.00 – 0.00		0	-0.00 – 0.00		0	-0.00 – 0.00		0	-0.00 – 0.00								
Male (ref = Female)	-0.01	-0.03 – -0.01	0.63	0.01	-0.02 – -0.04	0.71	0	-0.06 – -0.05	0.92	-0.03	-0.05 – -0.00	0.19	0.02	-0.02 – -0.06	0.66							
APOE status (ref = 0 alleles)		0.66			0.75			0.76			0.54			0.71								
1 allele	-0.01	-0.03 – -0.01		-0.02	-0.05 – -0.01		0.01	-0.05 – -0.06		0.01	-0.01 – -0.04		-0.01	-0.05 – -0.03								
2 alleles	0.01	-0.02 – -0.04		-0.01	-0.06 – -0.03		0.04	-0.03 – -0.12		-0.02	-0.06 – -0.02		-0.04	-0.10 – -0.02								

Observations 526 527 527 527 527 527 R² / adjusted R² 0.133 / 0.126 0.023 / 0.015 0.002 / -0.005 0.016 / 0.008 0.009 / 0.002

Table S4. Linear regression results for all plasma variables investigated by sex and baseline diagnosis.

Interleukin 18 pg/ml				Cortisol Cortisol ng/ml				C Reactive Protein ug/ml				Intercellular Adhesion Molecule ng/ml				Immunoglobulin E ng/ml				Interleukin 8 pg/ml			
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>	<i>Estimates</i>	<i>CI</i>	<i>adjusted p</i>		
(Intercept)	2.33	2.17 – 2.50	0.0001	0.08	1.96 – 2.20	0.01	-0.07	-0.56 – 0.41	0.0001	1.92	1.78 – 2.05	0.0001	1.6	1.11 – 2.09	0.0001	0.78	0.61 – 0.96	0.0001	certified by peer review) is the author/funder who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.	bioRxiv preprint doi: https://doi.org/10.1101/741777 ; this version posted August 23, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.			
AGE (years)	0	-0.00 – 0.00	0.9999	0	-0.00 – 0.00	0.9999	0.01	0.00 – 0.01	0.9999	0	-0.00 – 0.00	0.9999	0	-0.01 – 0.01	0.9999	0	0.00 – 0.01	0.9999	0	0.00 – 0.01	0.9999		
Male (ref = Female)	0.06	0.03 – 0.09	0.005	0.02	-0.01 – 0.04	0.47	-0.14	-0.24 – -0.05	0.03	-0.03	-0.06 – -0.01	0.08	0.25	0.15 – 0.34	<0.0001	0	-0.04 – 0.03	0.88					
Diagnosis (ref = CN)				0.63			0.01			0.08			0.27			0.88						0.35	
LMCI	0.04	-0.01 – 0.10		-0.02	-0.07 – -0.02		-0.26	-0.44 – -0.09		-0.01	-0.06 – -0.03		-0.01	-0.18 – -0.17		-0.04	-0.10 – -0.02						
AD	0.03	-0.03 – 0.10		0.03	-0.02 – -0.08		-0.22	-0.41 – -0.03		0.02	-0.03 – -0.08		-0.04	-0.23 – -0.16		0	-0.07 – -0.06						
Observations	527			527			526			527			527			527			527			527	
R^2 / adjusted R^2	0.032 / 0.025			0.034 / 0.026			0.043 / 0.036			0.029 / 0.021			0.050 / 0.043			0.027 / 0.020							

Table S4 (continued). Linear regression results for all plasma variables investigated by sex and baseline diagnosis.

CD 40 antigen ng/ml				Interleukin 16 pg/ml				Interleukin 3 ng/ml				Interleukin 6 receptor ng/ml				Immunoglobulin A mg/ml			
Predictors	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p	Estimates	CI	adjusted p				
(Intercept)	-0.56	-0.67 – -0.46		2.38	2.23 – 2.53		-1.62	-1.89 – -1.35		1.44	1.32 – 1.56		0.42	0.22 – 0.63					
AGE (years)	0.01	0.00 – 0.01		0	0.00 – 0.00		0	-0.00 – 0.00		0	-0.00 – 0.00		0	-0.00 – 0.00					
Male (ref = Female)	-0.01	-0.03 – 0.01	0.68	0.01	-0.02 – 0.04	0.63	-0.01	-0.06 – 0.05	0.52	-0.02	-0.05 – -0.00	0.19	0.02	-0.02 – 0.06	0.68				
Diagnosis (ref = CN)			0.08			0.08			0.75				0.63			0.84			
LMCI	-0.02	-0.05 – 0.02		-0.08	-0.13 – -0.02		-0.04	-0.14 – 0.06		-0.03	-0.08 – 0.01		0.03	-0.05 – 0.10					
AD	0.02	-0.02 – 0.06		-0.08	-0.14 – -0.02		-0.12	-0.22 – -0.01		-0.03	-0.08 – 0.02		0.02	-0.07 – 0.10					
Observations			526			527		527			527					527			
R ² / adjusted R ²	0.143 / 0.137				0.036 / 0.029				0.013 / 0.006				0.014 / 0.006				0.008 / -0.000		