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Research Report

A Proposal to Make Biomedical Research into Alzheimer's Disease More Democratic Following an International Survey with Researchers

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Abstract.

Background: Therapeutic research into Alzheimer's disease (AD) has been dominated by the amyloid cascade hypothesis (ACH) since the 1990s. However, targeting amyloid in AD patients has not yet resulted in highly significant disease-modifying effects. Furthermore, other promising theories of AD etiology exist.

Objective: We sought to directly investigate whether the ACH still dominates the opinions of researchers working on AD and explore the implications of this question for future directions of research.

Methods: During 2019, we undertook an international survey promoted with the help of the Alzheimer's Association with questions on theories and treatments of AD. Further efforts to promote a similar study in 2021 did not recruit a significant number of participants.

Results: 173 researchers took part in the 2019 survey, 22% of which held "pro-ACH" opinions, tended to have more publications, were more likely to be male, and over 60. Thus, pro-ACH may now be a minority opinion in the field but is nevertheless the hypothesis on which the most clinical trials are based, suggestive of a representation bias. Popular vote of all 173 participants suggested that lifestyle treatments and anti-tau drugs were a source of more therapeutic optimism than anti-amyloid treatments.

Conclusion: We propose a more democratic research structure which increases the likelihood that promising theories are published and funded fairly, promotes a broader scientific view of AD, and reduces the larger community's dependence on a fragile economic model.

Keywords: Alzheimer's disease, amyloid- β , dementia prevention, diversity in science, gender, lifestyle factors, lifestyle interventions, pharmaceutical industry, tau protein, women in science

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INTRODUCTION

Disagreement is an obvious fact of science and medicine, but how much is a good thing, and for how long, is worth asking. The community of clinicians and researchers working on Alzheimer's disease (AD) is an amalgam of distinct communities with different approaches to treating cognitive decline in the elderly. The dominant strategy for finding an AD cure since the 1990s has been targeting AD pathology (amyloid- β (A β) and tau proteins, with A β being the major therapeutic target in our contemporary period (Fig. 1, Liu et al., 2019: "up to 2019 ... the amyloid hypothesis was the most tested (22.3% of [human clinical] trials)" [1]). Writing in 2014, Hardy et al. open their paper by claiming that "There is no doubt that for the last 20 years, the ACH has dominated opinion about the aetiology and pathogenesis of AD, as well as guided the efforts to find treatments" [2]. Nevertheless, there has been a recent shift toward prevention and promotion of resilience to dementia through lifestyle interventions, as well as toward

other drug targets, given the uncertainty around the clinical utility of anti-A β strategies [1]. Indeed, this shift bears witness to the existence of a variety of promising theories for AD with compelling evidence in favor of them (two examples being microbes [3] and tau protein initiation [4]).

Scientists are guided in their decision-making by scientific data, but also by opinion. Zollman [5] studied how extreme beliefs and the unequal distribution of information within the research community can lead to "harmful homogeneity in science" (p. 19). The religious language used to describe debates around the suitability of therapeutic targets (defenders of A β and tau proteins as targets being termed BAPTISTS and TAUISTS, for example [6]), while perhaps used jokingly, is nevertheless suggestive of the possibility of extreme opinions in the AD community. An empirical study of productivity in AD research suggests that "a small percentage of researchers" [7] has access to a large portion of the research apparatus, and while this does not entail that *information* is distributed unequally, it does suggest the strong

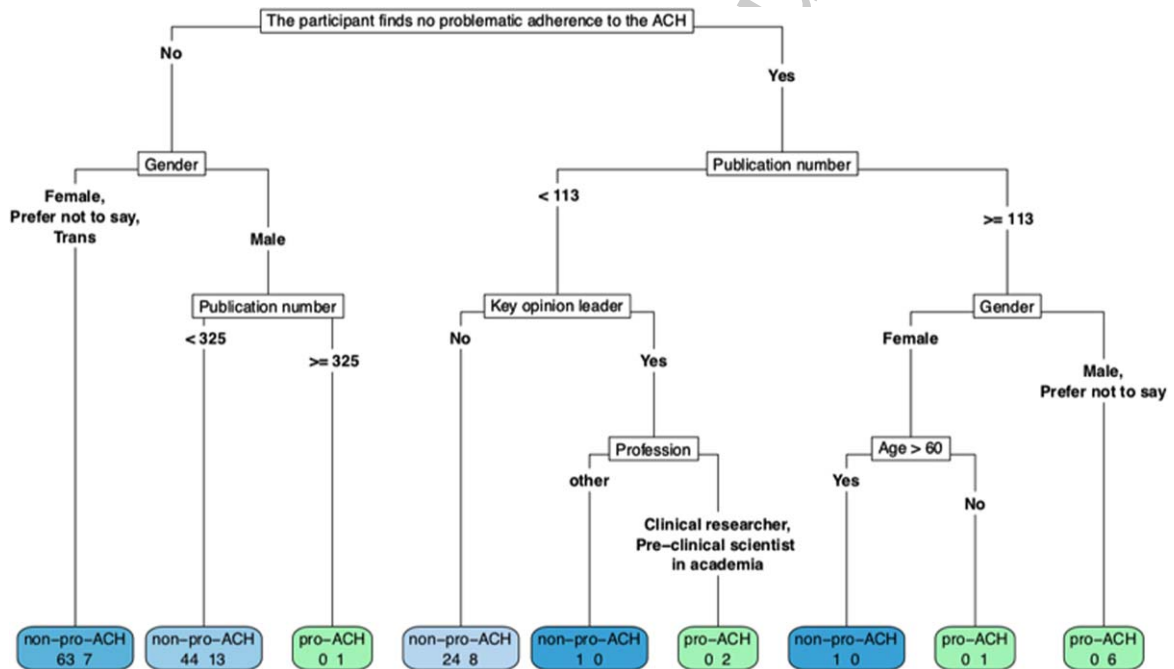


Fig. 1. A decision tree revealing pro-ACH/non-ACH differences according to the participant's view on whether or not there is problematic adherence to the ACH. We cut the depth of the tree to 5. Leave nodes (i.e., the final node in the figure) present the number of pro-ACH participants on the right and the number of non-ACH participants on the left. They are light blue to dark blue as a function of the proportion of non-ACH in the leave node, or they are light green to dark green as a function of the proportion of pro-ACH in the leave node. In the non-ACH group, 63 participants (47.37%) not identifying as male argue that there is problematic adherence to the ACH, compared to only 7 (18.42%) of the pro-ACH group with these characteristics. Conversely, on the other end of the scale, 6 males (or preferred not to say) of the pro-ACH group (15.79%) argued that there was no problematic adherence to the ACH and had more than 113 median publications. None of the non-ACH had this profile.

76 influence of an unrepresentative minority holding a
77 hierarchical sway over the broader direction of the
78 field, at least at the level of publications.

79 Furthermore, scientific “gatekeeping” in the form
80 of peer review and broader editorial policy offers the
81 advantage of improving the mean quality of published
82 science, yet also increases the risk that more uncon-
83 ventional work is rejected [8]. Indeed, critiques of
84 current funding and publishing models for biomed-
85 ical research exist beyond the AD field, arguing that
86 conformity to dominant models tends to lead to more
87 funding [9].

88 These conditions suggest there might well be
89 “harmful homogeneity” in AD research. However,
90 the presence of an influential minority suggests that
91 getting access to most researchers’ opinions about
92 AD should not be done via published literature, which
93 cannot adequately represent most researchers work-
94 ing on this disease. We therefore decided to opt for
95 direct access to researchers’ opinions about theories
96 and treatments of AD, creating the first anonymous
97 survey into researcher opinions towards theories and
98 treatments of AD. Firstly, we wanted to test Hunter
99 et al. [10]’s hypothesis of “two broad groups; those
100 that support the amyloid cascade hypothesis and
101 those that do not” (p. 254). Secondly, we tested the
102 constituent characteristics of the “pro-ACH” group,
103 before thirdly, looking at possible gender differences
104 in the popular vote toward treatments for AD at dif-
105 ferent disease stages.

106 METHODS

107 *Ethical approval*

108 The project received ethical approval from the
109 Research Ethics Community of *Université Paris*
110 *Descartes* and the data analysis complied with the
111 French *Commission nationale de l’informatique et*
112 *des libertés* (CNIL) guidelines. All the data were
113 anonymous and were analyzed in aggregate form. All
114 of the raw survey data are available as Supplementary
115 Material.

116 *Survey design and promotion*

117 Questions and responses comprised two cate-
118 gories: research (on theories and treatments of AD)
119 versus personal (age, profession, country of primary
120 affiliation, clinical versus academic researcher). All
121 questions were optional and multiple choice, based
122 on extensive literature review and consultation with

123 colleagues. The participant filled out the form by fol-
124 lowing the URL to the Google Forms sheet.

125 We used Twitter (the account of The Alzheimer’s
126 Association International Society to Advance
127 Alzheimer’s Research and Treatment “@ISTAART;”
128 and T.D.’s personal account, “@PhilAlz”) and a
129 poster at The Alzheimer’s Association International
130 Conference (AAIC) 2019 to promote the link to the
131 Google Forms to recruit survey participants between
132 January 1, 2019 and December 31, 2019. A second
133 wave of promotion was undertaken in January 2021,
134 but with less than 20 responders, thus only data from
135 2019 are analyzed herein.

136 *Hypothesis testing and statistical analysis*

137 Three hypotheses were tested concerning partici-
138 pant responses. Statistical analyses were performed
139 using R version 3.6.1 (R Foundation for Statistical
140 Computing, Vienna, Austria. URL [https://www.R-](https://www.R-project.org/)
141 [project.org/](https://www.R-project.org/)). Participant characteristics were com-
142 pared between the pro-ACH and non-ACH groups
143 using Wilcoxon-Mann-Whitney test for continuous
144 variables and Fisher’s exact test for categorical vari-
145 ables. Discrepancies in participant response numbers
146 were due to the optional nature of every question.

147 *Hypothesis 1: Pro-ACH responders will account* 148 *for the majority of the participants*

149 When participants were asked which categories
150 of drugs gave them hope for a treatment of AD, if
151 they answered “BACE inhibitors” and/or “Anti-A β
152 antibodies” (which we combine in Results as “ACH
153 drugs”) and also considered “A β physiology (produc-
154 tion, clearance, etc.)” to be the number 1 priority in
155 pre-clinical, early, or late stage AD, then they were
156 considered to be “pro-ACH.”

157 *Hypothesis 2: The ACH-group will have different* 158 *constitutive characteristics as compared to the* 159 *non-ACH group*

160 In order to describe the profiles of pro-ACH
161 and non-ACH survey participants, we performed
162 the Classification And Regression Tree (CART)
163 algorithm. The CART algorithm, also known as a
164 “decision tree”, is a non-parametric supervised tech-
165 nique that combines variables in such a way as to
166 best discriminate between two groups. We trained a
167 decision tree of depth 5 through entropy minimiza-
168 tion with characteristics such as age higher than 60;

Table 1

Differences in the constitutive characteristics and opinions towards the ACH of pro-ACH and non-ACH groups identified in the 173 survey participants. Gender differences were significant between the pro-ACH and non-ACH groups, with significantly more men being pro-ACH. Taken together, these results suggest an association between having pro-ACH opinions and more publications, industry money, and self-identifying as a key opinion leader. [‡]Fisher's exact test was used to compare groups for categorical variables

	all N = 173	Non-ACH N = 133 (76.88%)	pro-ACH N = 38 (21.97%)	<i>p</i> [‡]
age > 60 y	19 (11.05%)	10 (7.52%)	8 (21.05%)	0.031*
Gender				0.035*
<i>Female</i>	83 (49.70%)	71 (55.47%)	12 (31.58%)	
<i>Male</i>	80 (47.90%)	54 (42.19%)	25 (65.79%)	
<i>Prefer not to say</i>	3 (1.80%)	2 (1.56%)	1 (2.63%)	
<i>Trans</i>	1 (0.60%)	1 (0.78%)	0 (0.00%)	
Continent of Major Affiliation				0.243
<i>North Africa</i>	1 (0.60%)	0 (0.00%)	0 (0.00%)	
<i>North America</i>	101 (60.12%)	78 (60.47%)	23 (60.53%)	
<i>South America</i>	11 (6.55%)	10 (7.75%)	1 (2.63%)	
<i>Asia</i>	9 (5.36%)	9 (6.98%)	0 (0.00%)	
<i>Europe</i>	40 (23.81%)	28 (21.71%)	12 (31.58%)	
<i>Oceania</i>	6 (3.57%)	4 (3.10%)	2 (5.26%)	
publications number > 100	24 (14.04%)	14 (10.53%)	10 (27.03%)	0.016*
Profession				
<i>Clinical researcher</i>	67 (38.73%)	51 (38.35%)	15 (39.47%)	0.236
<i>other</i>	18 (10.40%)	16 (12.03%)	1 (2.63%)	
<i>Pre-clinical scientist in academia</i>	88 (50.87%)	66 (49.62%)	22 (57.89%)	
Key Opinion Leader (Yes)	26 (15.48%)	16 (12.40%)	10 (26.32%)	0.045*
Received money from pharma company (Yes)	29 (16.86%)	18 (13.53%)	11 (28.95%)	0.047*
<i>Questions regarding the ACH's validity</i>				
<i>ACH drugs are NOT a source of optimism for treating human AD.</i>	86 (54.09%)	86 (71.67%)	0 (0.00%)	< 0.001*
<i>Beta-amyloid is NOT the #1 therapeutic priority either at preclinical, early, or late-stage AD.</i>	119 (69.59%)	119 (90.15%)	0 (0.00%)	< 0.001*
There is problematic adherence to the ACH from either industry, academia, associations or funding bodies	125 (73.96%)	105 (80.15%)	20 (54.05%)	0.002*
Moving forwards (2019–), the ACH is a useful tool to guide research.	60 (35.50%)	35 (26.92%)	24 (63.16%)	< 0.001*
Agree with Tanzi (2015): “The clinical trials are failing the hypothesis, the hypothesis is not failing the trial.”	76 (44.71%)	45 (34.35%)	30 (78.95%)	< 0.001*
Agree with Tanzi (2017): “we need to find people with amyloid buildup on their brain early” and target it.	89 (52.35%)	56 (42.75%)	32 (84.21%)	< 0.001*
Agree with Davies (2016): “we’re flogging a dead horse” (A-beta)	54 (31.76%)	52 (39.69%)	2 (5.26%)	< 0.001*
Agree with Herrup (2015): “clinging to an inaccurate disease model is the option we should fear most.”	82 (48.52%)	75 (57.69%)	7 (18.42%)	< 0.001*

gender; country: USA; number of publications; clinical researcher (versus academic); key opinion leader (KOL); has received money from the pharmaceutical industry; whether or not the researcher thinks that “there is problematic adherence to the ACH from either industry, academia, associations or funding bodies”. We used the term adherence so as to insist upon the ACH’s ability to guide research.

Hypothesis 3: There will be gender differences in the popular vote towards treatments of AD

We investigated the top three therapeutic targets at pre-clinical, early-stage, and established AD according to popular vote of all the survey participants, pro-ACH and non-ACH taken together. Furthermore,

if there are gender differences to be found in the pro-ACH/non-ACH groups, we might expect to find gender differences in the popular vote. Only participants identifying as M/F were included in the gender differences so as to use comparable group sizes for significance testing ($n = 7$ of “trans/prefer not to say/other”).

RESULTS

One hundred and seventy-three participants from across the world filled out the questionnaire, with a median age of 35, 83 (49.7%) being women. We identified 38 (22.0%) “pro-ACH” participants, the majority (65.8%) of whom were men (Table 1).

Table 2

The popular vote of all researchers (pro-ACH and non-ACH taken together) toward therapeutic priorities in AD research, tabulated according to participants' gender. Concerning pharmacological treatments, anti-tau drugs offered more optimism than drug classes inspired by the ACH (anti-A β antibodies and/or BACE inhibitors). The top three therapeutic targets at preclinical, prodromal, and established AD were also investigated. Lifestyle interventions were a top-3 therapeutic priority at all stages of AD. Taken as a whole, the data suggest a favorable opinion regarding lifestyle factors and tau protein intervention. Gender differences in therapeutic priority were only significant for preclinical AD, with significantly more males arguing in favor of anti-A β strategies at this stage. [‡]Fisher's exact test was used to compare groups for categorical variables

	all N = 173	Female N = 83 (49.70%)	Male N = 80 (47.90%)	p^{\ddagger}
<i>Optimism towards the following drugs</i>				
Anti-tau	97 (61.01%)	50 (66.67%)	40 (53.33%)	0.133
Anti-AB antibodies	62 (38.99%)	24 (32.00%)	33 (44.00%)	0.178
BACE inhibitors	31 (19.50%)	15 (20.00%)	12 (16.00%)	0.671
<i>#1 Therapeutic Priority in preclinical AD</i>				
Lifestyle factors (diet, smoking, etc.)	74 (43.53%)	39 (46.99%)	31 (39.74%)	0.020*
A β physiology (production, clearance, etc.)	33 (19.41%)	10 (12.05%)	22 (28.21%)	
Inflammation, Microglia, and Astrocytes	22 (12.94%)	10 (12.05%)	11 (14.10%)	
<i>#1 Therapeutic Priority in prodromal AD</i>				
Lifestyle factors (diet, smoking, etc.)	49 (31.01%)	24 (32.00%)	22 (29.73%)	0.060
Tau and NFTs	40 (25.32%)	22 (29.33%)	15 (20.27%)	
Inflammation	26 (16.46%)	13 (17.33%)	11 (14.86%)	
<i>#1 Therapeutic Priority in established AD</i>				
Tau and NFTs	44 (28.21%)	19 (25.68%)	21 (28.38%)	0.928
Lifestyle factors (diet, smoking, etc.)	38 (24.36%)	20 (27.03%)	17 (22.97%)	
Inflammation, Microglia, and Astrocytes	29 (18.59%)	14 (18.92%)	13 (17.57%)	

196 Pro-ACH participants were more likely to report
197 writing more than 100 publications (27.0% versus
198 10.5% in the non-ACH group, $p=0.016$), to be a
199 self-reported KOL (26.3% versus 12.4%, $p=0.045$),
200 to be aged over 60 (21.1% versus 7.5%, $p=0.031$),
201 and to have received money from the pharmaceuti-
202 cal industry (29.0% versus 13.5%, $p=0.047$), than
203 non-ACH participants. However, median age group
204 differences did not reach significance. In the non-
205 ACH group, 80.2% argued that there was problematic
206 adherence to the ACH from within and outside the sci-
207 entific community, versus 54.1% of pro-ACH (54.1%
208 versus 80.2%, $p=0.002$). No difference was found for
209 country or profession.

210 Concerning the lack of therapeutic progress made
211 in AD research, 79.0% of pro-ACH (versus 34.4% of
212 non-pro, $p<0.001$) agreed with Tanzi [11] that “the
213 clinical trials are failing the hypothesis, the hypothe-
214 sis is not failing the trial.” 84.2% (versus 42.8%,
215 $p<0.001$) agreed with Tanzi [12] in favor of earlier
216 anti-amyloid strategies in humans, only 5.3% (versus
217 39.7% of non-ACH) agreeing with Davies [13] that
218 such strategies were akin to “flogging a dead horse”
219 when referring to targeting amyloid- β . As regards the
220 ACH's future, 18.4% of pro-ACH (versus 57.7% of
221 non-ACH, $p<0.001$) agreed with Herrup [14] that
222 “clinging to an inaccurate disease model” was the
223 worst option for the future facing the community.

224 Finally, in order to better discern pro-ACH versus
225 non-ACH opinions, we used a decision tree (Fig. 1).

226 We also studied the popular vote of all participants
227 towards treatments and possible gender differences to
228 be found in it. Anti-tau treatments were the highest
229 source of optimism (61.0% of participants), fol-
230 lowed by anti-A β antibodies (39.0%) and BACE
231 inhibitors (19.5%). No significant gender differences
232 were found in responses concerning optimism about
233 drug types.

234 Lifestyle factors were the top therapeutic priority in
235 pre-clinical and prodromal AD (winning 43.5% and
236 31.0% of the popular vote, respectively). In preclini-
237 cal AD, A β (19.4%) and inflammation (12.9%) were
238 the next most popular targets, and in prodromal AD,
239 tau and neurofibrillary tangles (NFTs) (25.0%), A β
240 and inflammation (15.2% and 16.5% respectively)
241 the next most popular. In established AD, tau and
242 NFTs were the highest therapeutic priority (28.2%
243 of the popular vote), followed by lifestyle factors
244 (24.4%) and inflammation (18.6%). Concerning gen-
245 der differences, only at preclinical AD did gender
246 differences reach significance ($p<0.02$), with men
247 voting comparatively less for lifestyle factors (39.7%
248 versus 47.0% for women), and more for A β (28.2%
249 versus 12.1% for women), probably a reflection of
250 the gender division between pro-ACH and non-ACH
251 opinions.

DISCUSSION

According to our international survey with 173 participants, pro-ACH opinions did not represent the dominant opinion of researchers working on AD as of 2019; approximately 22% of researchers belonged to what we defined as the pro-ACH group. This group tended to argue that the ACH was a useful tool to guide research, and that there was therapeutic interest in the early targeting of A β , as opposed to the other “broad group” of researchers [10]. Furthermore, more publication and industrial money is to be found more in the pro-ACH group than in the non-ACH group.

Nevertheless, the fact that more than half of “pro-ACH” participants agree that there is problematic adherence to the ACH in the larger community (54% versus 80% of non-ACH) is consistent with certain researchers that we have interviewed more extensively (TD, AP): they are not ready to let go of the ACH, continue to rely on certain heuristic aspects of it, and at the same time, they are slowly embarking on other paths. This suggests that community-wide movements away from the ACH are more incremental than revolutionary.

Finally, women were under-represented in the pro-ACH group, representing 32% of the pro-ACH and 55% of the non-ACH group respectively. Concerning gender and age differences, it must not be forgotten that the social structure of biomedical science is hierarchical, with research strategies being mostly directed by principal investigators, i.e., experienced medical doctors and scientists. Differences observed in gender and age may therefore not be related to these variables so much as to the social positions occupied by doctors in the research hierarchy, in which older males are over-represented. Moreover, gender differences themselves may partly have been explained by age, since there were more over 60s to be found in the group of men (16.3% versus 4.8%). Our anecdotal observations (TD, SE) from *AlzForum*, an influential online community for AD researchers, suggest that the majority of influential commentators on current affairs in AD research tend to be men in these dominant social positions.

When looking at the popular vote in this survey, anti-tau compounds were a source of greater therapeutic optimism than anti-amyloid strategies, and lifestyle factors were considered to be a top therapeutic priority at all stages of human AD. We will now discuss one way of making AD research more faithful to popular vote. Nevertheless, before we do

so, it is worth noting that there are major limitations to this study.

Study limitations

Firstly, 173 Twitter-using researchers represent a small minority of AD researchers (for example, AAIC in Los Angeles in 2019 alone counted 5,700 researchers). And this small sample may have been biased: only those with a strong opinion responding and giving theirs. Thus, the generalizability of our findings may be low. Forcing the research community into polarized groups (“pro-ACH” versus the rest) may not reflect the nuance in opinions that researchers have toward theories which can be studied thanks to other methods, such as bibliometrics [15]. This polarization is aggravated by the fact that quotes taken out of context from the scientific and lay literature (e.g., from Rudolph Tanzi) were used as sources of survey questions.

Concerning self-identification of individuals, our gender categories were highly limited, and our relatively small sample did not allow us to undertake statistical analysis on the contributions of non-traditional or non-conforming gender identities to the popular vote on treatments for AD. It is clear that there is need for greater work on “accountability, justice and representation” for gender minorities in STEM [16]. Furthermore, we did not ask questions on ethnicity, which other STEM researchers are indeed asking so as to “boost diversity in science” [17]. Finally, we did not offer an explicit definition of a “key opinion leader,” an ambiguous term whose value to these results is debatable because of the fact we let participants self-identify as KOL or not.

Moreover, as regards the ACH, just as our results suggest that there is some diversity of opinion within the pro-ACH group (e.g., their view of possible problematic adherence to the ACH), it is also clear that non-ACH opinions are not of one kind: some researchers are vocally in favor of “rejecting the amyloid cascade hypothesis” [14] and would be more aptly described as “anti-ACH.”

Finally, these results are time-sensitive: as different results from clinical trials and other studies are published, so do opinions change toward theories and treatments. The fact that our final round of survey promotion was unsuccessful warrants further analysis into researchers’ susceptibility to change their opinion on a scientific topic over a short period of time. The lower participation in 2021 could be due to current events in the field (see Conclusion),

352 complications due to the Covid-19 pandemic, or sim- 402
353 ply the same participant population not wishing to 403
354 undertake another similar survey. However, any such 404
355 explanatory hypothesis would be highly speculative, 405
356 and the issues being discussed in this paper (i.e., the 406
357 possibility that there might be publishing and funding 407
358 advantages of supporting the ACH) are worthy of fur- 408
359 ther discussion and investigation. Limitations on the 409
360 speed with which such research can be designed, eth- 410
361 ically approved, undertaken, and published, should 411
362 be taken into account in further studies with similar 412
363 objectives. 413

364 *A proposal to make biomedical research into AD* 414
365 *more democratic* 415

366 It is well-known that biomedical science, as a 417
367 complex social activity, is guided by non-scientific 418
368 factors, such as economic interests [18]. Reiss and 419
369 Kitcher [19] argue that well-ordered biomedical sci- 420
370 ence should follow the “fair-share principle,” where 421
371 the amount of global funds spent on different dis- 422
372 eases should be proportional to the suffering caused 423
373 by them on a global scale. By analogy, we might 424
374 ask: within the study of a single disease, how should 425
375 resources best be dedicated to testing hypotheses and 426
376 developing therapies based on them according to a 427
377 “fair-share principle”? In other words, how can we 428
378 make sure that promising theories of AD get their 429
379 fair share of study and funding? 430

380 Solving this incredibly difficult problem is well 431
381 beyond the scope of this article, but we will offer a 432
382 sketch of a pro-democracy argument based on “crowd 433
383 wisdom,” the empirical finding that informed col- 434
384 lectives outperform individuals in estimating true 435
385 values of different variables, before underlining two 436
386 tragedies if the AD community does not succeed in 437
387 organizing science better. 438

388 Kitcher [20, 21] argues in favor of a democratic 439
389 deliberation process: taking the points of view of dif- 440
390 ferent segments of the community and attempting to 441
391 guide research according to them. This does not *have* 442
392 to mean a majority vote, but the phenomenon known 443
393 as the wisdom of the crowd [22] suggests that the 444
394 average value of multiple estimates tends to be more 445
395 accurate than any one single estimate. Therefore, lis- 446
396 tening to the popular vote of researchers—at fora such 447
397 as the yearly AAIC, and pooling a certain percentage 448
398 of available funding towards the therapeutic leads 449
399 suggested by popular vote—would mean drawing 450
400 on many thousands of collective years of experience 451
401 and perspective, which could lead to more accurate 452

402 estimates of the causes of AD, and the best treatments 403
404 to pursue. There is also increasing research being 405
406 done with dementia patients in a co-research role in 407
408 gerontology research (for example [23]); there is also 409
410 much unexplored scope for including the patient com- 411
412 munity in deliberation processes concerning curative 413
414 and preventive research into AD, and popular vote 415
416 could also be used here.

417 The major idea defended here is that projects 418
419 should be funded in a way that better represents the 420
421 plurality of therapeutic leads offered by the research 422
423 community. A yearly popular vote could be one step 424
425 in that direction. But this leaves many questions open 426
427 which we cannot definitively answer in one article, 428
429 including, but not limited to the following: 430

431 *How could we improve representation on fund-* 417
432 *ing bodies and editorial boards, including a role* 418
433 *for the patient community?* 419

434 *Upon what kinds of evidence should publica-* 420
435 *tion and funding decisions be based so that both* 421
436 *scientific pluralism and plausibility are guaran-* 422
437 *teed in AD research according to a fair-share* 423
438 *principle?* 424

439 *What kind of funding model would be most* 425
440 *suited to a more democratic approach: private* 426
441 *and/or public ventures?* 427

442 *Are there some domains and methods within* 428
443 *biomedical science might be particularly under* 429
444 *the influence of monopolized ways of think-* 430
445 *ing? (e.g., at the level of pre-clinical or clinical* 431
446 *research?) Could publication and funding quo-* 432
447 *tas be used to make monopolized domains more* 433
448 *inclusive?* 434

449 *How, and to what extent, could the themes of* 435
450 *calls for contributions and projects by publish-* 436
451 *ers and funders be broadened on a long-term,* 437
452 *community-wide scale?* 438

439 Furthermore, a more democratic model itself 440
441 would not be perfect, particularly if it were taken to 442
443 the extreme of eroding individual expertise, which 444
445 is and should remain a cornerstone of rigorous sci- 446
447 ence. Instead, the model we propose serves to reduce 448
449 monopoly, and thereby take any possible institu- 450
451 tionalized brakes off the contributions of individual 452
452 scientists.

453 In any case, if research cannot become better orga- 447
454 nized, we anticipate two major tragedies. The first 448
455 concerns the survival of the fragile economic model 449
456 underlying therapeutic research into AD, without 450
457 which patients will never receive disease-modifying 451
458 treatment. The second concerns science itself. 452

Indeed, the current high-risk model encourages the opposition between patient need and return on investment for innovators. Bringing an AD drug to market is estimated to cost \$5.6 billion [24]. The developer of the first monopolized disease-modifying treatment of AD would stand to gain an astronomical return on their major investment. Conversely, when a clinical trial of a much-anticipated AD treatment fails, the market value of the pharmaceutical company that developed it loses as much as 40% overnight, as in the case of Eli Lilly and solanezumab [13]. In January 2018, the pharmaceutical company Pfizer decided to stop its research on AD and Parkinson's disease by laying off 300 researchers due to numerous drug failures amid a dismal context for research on neurodegenerative diseases: pulling out was part of "an exercise to reallocate spend across our portfolio," according to the company [25]. It is not clear what the future of AD research looks like, but it is fragile and, in its current state, mostly dependent on amyloid being a viable target, with millions of patients and families living in hope. By ensuring that other promising theories are funded, at a community-wide level, it would allow bets to be hedged against the possibility that the ACH does not deliver on its promises.

The second tragedy, done against science itself and those individuals who defend it, is "epistemic injustice," a term coined by philosopher Miranda Fricker as "wrong done to someone specifically in their capacity as a knower" [26]. Fricker draws on examples from literature and history where factors such as race and gender have led to points of view being ignored and condemned. Within AD research, there are surely examples of intellectually honest researchers defending controversial hypotheses of AD who have struggled to get data published, receive funding, and retain their place within academia. In other words, certain hypotheses might be rejected not because of scientific argument but rather the social structure of the field of biomedical research. We finish by noting that the results from our small sample tentatively suggest that the majority of women do not support the ACH and may therefore be particularly vulnerable to the negative consequences of a community gatekeeping bias. Taking the example of hypotheses concerning the role of microbes in AD [3], Fig. 1 from Liu et al. (2019) showed that "... up to 2019 ... 0.5% of trials tested the virus hypothesis" [1]. Concerning this "fringe theory ... now, researchers are taking it seriously" [27], but the fact that up to 2019 only 1 in 200 clinical trials were dedicated to testing a direct viral contribution

to AD, does beg the question: are theories of AD being funded according to fair-share principle? Ruth Itzhaki, first author on the previously cited [3] editorial on microbes in AD, has described "a series of battles ... awful problems getting [research] published" [28]. This example does point to the possibility of epistemic injustice in AD research and suggests the existence of perspectives whose contribution to improving the lives of AD patients has not yet been fully taken into account. This seems like community-wide oversight, since the perspectives of marginalized individuals in institutionalized social structures may offer particularly insightful contributions to research, since they may recognize patterns in the world that those in more dominant groups may be blinded to [29].

CONCLUSION

The recent, controversial accelerated FDA approval of Biogen/Eisai's Aducanumab for use in mild AD is a testament to the influence of the ACH and its defenders on the scientific and wider community. The tentative results found in our survey suggest that there is a complex scientific landscape behind the scenes which risks becoming even more polarized following such divisive decision-making [30]. Given the hardships of the research community in finding a disease-modifying treatment for AD, we argue that further efforts should be made to explore democratic solutions to overcome research monopolies so that their potential consequences for patients and scientists can be reduced, and clinically useful treatments for AD be found as soon as possible. It appears that the optimism toward the ACH which has motivated industry and the recent FDA decision may well not be shared by the majority of researchers working on AD. This study offers one tool to study this otherwise silent majority, whose collective wisdom, we argue, could and should be taken into further consideration for the future of vital research into this devastating, complex disease.

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CONFLICT OF INTEREST

Timothy Daly, Marion Houot, Anouk Barberousse, and Amélie Petit declare no conflicts of interest. Stéphane Epelbaum has received consulting fees from Biogen, Roche, Eisai and GE Healthcare.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/ADR-210030>.

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