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ARTICLE

Fear of Dementia and the Obligation to Provide Aggregate Research Results to Study Participants

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Abstract

A general obligation to make aggregate research results available to participants has been widely supported in the bioethics literature. However, dementia research presents several challenges to this perspective, particularly because of the fear associated with developing dementia. The authors argue that considerations of respect for persons, beneficence, and justice fail to justify an obligation to make aggregate research results available to participants in dementia research. Nevertheless, there are positive reasons in favor of making aggregate research results available; when the decision is made to do so, it is critical that a clear strategy for communicating results is developed, including what support will be provided to participants receiving aggregate research results.

Keywords: Dementia; Alzheimer's disease; biomarkers; imaging; ethics; research results

Introduction

There are currently more than 55 million people living with dementia worldwide, with this number expected to reach 75 million by 2030, and 135 million by 2050.[1] Demographic shifts are primarily responsible for this increase, particularly in low and middle-income countries, as the global population of people 60 and older continues to increase at an unprecedented rate. As of 2015, 63% of people with dementia live in low and middle-income countries, where access to support services and care is limited.[2] Because the incidence of dementia increases exponentially with age—doubling every 5 years from 1% incidence at age 65—even slight delays in disease onset could have a significant impact on the public health burden of dementia-related disability.[3]

Although dementia can arise from a variety of diseases and injuries affecting the brain, the most common cause, accounting for 60–70% of dementia cases, is Alzheimer's disease (AD).[4] Despite significant advances in the understanding of AD biology, and significant investment in drug development, there remains no cure for AD, and no effective pharmacological treatment to slow progression.

Accordingly, attention has shifted towards "secondary prevention": modification of the pathological processes that occur before the onset of symptoms. A growing body of evidence, based on biomarker and imaging findings (e.g., levels of amyloid-β in cerebrospinal fluid or on PET brain imaging), suggests that AD pathophysiology begins many years, even decades, prior to the clinical expression of the disease.[5,6] This asymptomatic phase, referred to as *pre-clinical AD*, represents an opportunity to intervene at earlier stages of the disease continuum in the hopes of delaying the onset of functional and clinical decline, and has become a major research focus.

However, the clinical validity of biomarker information for asymptomatic individuals is still open to question. It remains unclear what proportion of individuals with biomarkers indicative of AD pathology will progress to a symptomatic stage of the disease. Based on post-mortem analysis, there is a significant proportion of individuals with evidence of AD pathophysiology in their brains, but who did not have evidence of clinically expressed disease prior to death.[7] This is because the clinical expression of AD is likely based on a complex interaction of factors, including brain lesions, but also an individual's age and cognitive abilities ("cognitive reserve"), as well as genetic, environmental, and lifestyle factors.[8]

This raises the challenging question of what should be disclosed to participants in dementia research, but who have not shown any symptoms of dementia. On the one hand, the lack of robust predictive value at the individual level, and the potential psychosocial harms of learning one's risk status in the absence of effective preventive or therapeutic options have led to a recommendation against communicating risk information.[9] Similarly, there is concern about excessive testing for AD—brought on by the routine communication of risk factors or changes in cognition and brain health due to known risk factors (e.g., family history of dementia)—resulting in unnecessary treatment of age-related cognitive changes.[10] On the other hand, a significant proportion of research participants (50–90%) are interested in receiving information about their risk of dementia,[11,12,13,14] or, if they know they are at risk, are interested to learn about their current health status. Participants' interest, however, tends to decrease as their understanding of the uncertainty and limited generalizability of risk information increases.[15]

Although the disclosure of individual biomarker results of the kind described above to research participants without symptoms of dementia remains contested, the disclosure of aggregate research results is generally considered far less controversial. Aggregate research results—sometimes referred to as *group-* or *population-level results*—are findings that represent the study population, rather than results applicable to individual participants. Making aggregate research results available to participants has been widely supported by health researchers and bioethicists,[16,17,18,19,20] and recommended by international ethical guidelines.[21] Making these results available is argued to follow from three principles of research ethics: respect for persons, beneficence/non-maleficence, and justice. However, dementia research presents challenges to the generalized obligation to make aggregate results available, specifically due to fear of dementia. It is these challenges concerning the feedback of aggregate results that we will focus on in this paper.

Fear of Dementia

Studies have shown that for a significant portion of the population (26–39%), dementia is the most feared medical diagnosis, surpassing even cancer.[22] Concern about developing dementia, combined with a general lack of knowledge about AD and other types of dementia, has been argued to contribute to "dementia worry"[23,24,25] or "dementia-related anxiety (DRA)".[26] Kessler et al. describe dementia worry as "an emotional response to the perceived threat of developing dementia, independent of chronological age or cognitive status."[27] Those with high levels of dementia worry report higher concern about current memory functioning, endorse more beliefs that they may develop dementia in the future, and report higher levels of depressive symptoms than those without dementia worry.[28] They also demonstrate decreased life satisfaction and psychological well-being.[29]

Studies have also shown that dementia worry is associated with poorer cognitive functioning. For example, Lineweaver et al.[30] showed that middle-aged and older adults' memory performance and memory self-assessment were negatively affected if they learned that they had the apolipoprotein E (APOE) ε4 allele risk factor for AD. Participants who knew they had the APOE ε4 allele performed worse on objective memory tasks and memory self-assessment than participants who carried the allele but did not know it. Adrianna Kinzer and Julie Suhr showed that dementia worry moderated the relationship between actual cognitive impairment and subjective memory concerns, finding that cognitively healthy participants with high dementia worry reported as many memory concerns as cognitively impaired participants.[31] Dementia worry is also significantly related to decreased neuropsychological performance on measures of executive function in healthy older adults.[32,33]

Fears related to the development of AD can also have a compounding effect, insofar as they lead to the avoidance of behaviors that are known to be protective against dementia. For example, individuals concerned about memory loss may avoid cognitively or socially demanding situations, despite the fact that cognitive stimulation and social integration have neuroprotective and compensatory effects, even in people with high genetic risk of developing dementia.[34] Consistent with this, Farina et al. showed that higher levels of fear and avoidance about memory loss were associated with reduced ability to participate in social roles and activities among community-dwelling older adults.[35]

This association between fear of dementia and negative mental, social, and physical outcomes complicates the question of whether feeding back aggregate research findings is beneficial or harmful to participants. Psychological models of health anxiety development cite both experiential factors (e.g., learning about a disease from public education campaigns, observing the disease in a family member, or participating in dementia research) and premorbid individual differences (e.g., anxiety, depression, neuroticism, conscientiousness, belief in negative aging stereotypes) as influencing the development of dementia worry.[36]

These factors raise the possibility that aggregate level results could be interpreted as having individual implications, contribute to dementia worry and, thus, may be harmful to participants. Indeed, the *belief* that one is at heightened risk of dementia, rather than one's actual risk of dementia, significantly associates with impairments in cognitive performance in the studies described above (cf. the Thomas Theorem: "If a person perceives a situation as real, it is real in its consequences"). Aggregate results that show brain and cognitive decline in asymptomatic individuals at risk for future dementia may lead participants to infer that they are individually experiencing decline, even in the absence of individualized information.

Concerns about cognitive decline may also lead to the misattribution of normal age-related cognitive changes. This could in turn contribute to misdiagnosis of mild cognitive impairment or early dementia, inappropriate treatment, and missed opportunities for effective treatment of other conditions contributing to the subjective sense of cognitive decline.[37] In a recent review of studies involving people presenting to memory clinics, McWhirter et al. found that nearly one quarter (24%) received a diagnosis consistent with functional cognitive disorder (FCD): a condition whereby cognitive symptoms are caused by functional changes rather than a degenerative brain disease.[38] Such patients, the authors argue, are at risk of harm due to false positive predictions of future decline.

Furthermore, the feedback of aggregate results, when combined with the potential for dementia worry, could lead to a confounding factor in longitudinal studies. Prospective cohort studies of candidate dementia biomarkers in asymptomatic individuals, such as the PREVENT dementia study,[39] collect a range of biological, psychological, and behavioral measurements from participants longitudinally, often over the course of several years. These studies may seek to recruit members of the study population for subsequent follow-up research after the completion of the cross-sectional data collection. If knowledge of aggregate results leads some participants to experience behavioral or cognitive changes brought on by dementia worry, subsequent research involving these participants may be biased. Accordingly, research is required to determine whether and to what extent disclosure of aggregate research results impacts fear of dementia.

Ethical Principles for Disclosure of Aggregate Research Results

Respect for Persons

It is broadly accepted in the bioethics literature that researchers ought to make aggregate results available to research participants. Conrad Fernandez et al.[40] argue that the principle of respect for persons grounds an obligation to offer aggregate research results to participants in a clear and understandable manner, at the conclusion of the study. This is because, they maintain, the act of offering aggregate results "avoids treating persons solely as a means to an end." The obligation to avoid treating others as a mere means has its roots in the philosophy of Immanuel Kant (although there is debate regarding precisely what it is to treat another "merely as a means.") Roughly, and departing somewhat from Kant's notion, to treat

someone as a mere means is to use them and regard them as a "mere instrument or tool: someone whose well-being and moral claims we ignore, and whom we would treat in whatever ways would best achieve our aims."[41] Treating a research participant as a "mere means" to the ends of research, then, is morally wrong insofar as it does not respect the participant's own aims in participating in research.

The principle of respect for persons attempts to capture the basic ethical conviction that individuals should be treated as autonomous agents, capable of deliberation about their own values and ends, and of acting on the basis of these deliberations. Respecting autonomy is to give weight to the considered opinions and judgments of autonomous persons, and refrain from obstructing their actions (unless they are harmful to others). Accordingly, respect for autonomy can be understood as implying a negative obligation of non-interference in the autonomous decisions of others, as well as a positive obligation to foster autonomous decision-making, including by increasing the options available to persons, or providing them with information material to their decision.[42]

Whether respect for persons generates an obligation to make aggregate research results available to participants, however, is contested. For example, Shalowitz and Miller claim that "it would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information…derived from their participation in research."[43] Conversely, Meltzer argues that researchers show respect for participants by disclosing the terms of the research and allowing them to choose for themselves whether they want to enroll.[44] Respect for persons means treating participants as self-determining agents and does not require researchers to account for participant preferences (including disclosure) when designing a research study. Prospective participants can choose whether to participate, and this is sufficient to show respect for their autonomy.

Meltzer is correct that a participant might freely consent to participate in research in which aggregate results are not returned, and thus, that such research does not run afoul of the negative obligation to respect autonomy. However, it may fall short of the positive obligation to promote autonomy. It could be argued that failure to make aggregate results available unjustifiably constrains the range of options open to the participant. Further, withholding this information might affect the autonomy of future decisions influenced by the presence (or lack) of health information, particularly if these aggregate results have individual implications for the participant. Conversely, if a participant draws unjustified conclusions about their health status on the basis of research findings, this may actually detract from their ability to act autonomously. This can be avoided if the disclosure is accompanied by an adequate explanation of the (limited) clinical value of the results, and the extent to which these results should, or should not, impact treatment.

Of course, the obligation to respect participant autonomy is not absolute. It can be overridden by competing moral considerations, including the possibility of harm to others, or when respecting autonomy requires the use of a scarce resource. Whether aggregate results should be made available to participants depends on an accounting of each of these considerations. For example, aggregate research findings with clear clinical utility, or that have robust predictive value at the individual level ought to be made available, because this information might inform a participant's rational decision-making about their care and has a high likelihood of providing benefit. Conversely, some aggregate results may be stigmatizing to certain communities, or involve a feedback procedure that is highly resource intensive. For example, it has been argued that aggregate-level genomic data may be capable of uniquely identifying individual communities, and predictions made about trait prevalence within those communities, which may lead to discrimination or even violence.[45] Alternatively, there are some cases in which aggregate research results may not be fully known until years after the close of a research study, at which time there may no longer be financial resources available for feedback.[46] In these sorts of cases, the value of showing respect for participant autonomy may not be sufficient to require making aggregate results available. Accordingly, we need to look more closely at the potential harms and benefits of making aggregate results of dementia research available, especially considering the prospect of dementia fear.

Beneficence and Non-Maleficence

Numerous commentators have argued that researchers have an obligation to promote the well-being of participants, and that this obligation might justify making research results available. Whether this obligation requires making aggregate results available to participants depends on the potential benefit, as well as the potential harms, of disclosure. On the one hand, as described above, aggregate research results may have health implications for individual participants. For example, group findings of early changes in the brain and cognition with known risk for late-life dementia could be interpreted by individual participants as indicative of their own health deterioration, and thus provide an impetus for altering health behaviors. Participants may also find the disclosure of aggregate results beneficial even if there is no clinical action that can be taken. For example, studies have shown that participants recognize a number of reasons to receive genetic information about AD risk beyond clinical concerns, including altruism, having knowledge for the sake of knowledge or for potential future uses, communicating risk to family members, having a sense of control, improving quality of life, and protecting against discrimination.[47] Insofar as aggregate research results are interpreted as having individual implications, similar benefits may result from making these results available. On the other hand, it may also cause negative psychological effects, including dementia worry and associated stress, anxiety, or depression, that can affect the participant's sense of self or future. Therefore, it is also possible that the provision of aggregate research results is associated with an unfavorable balance of potential harms and benefits.

Justice

The principle of justice holds that there should be fairness in the distribution of the benefits and burdens of research. Because the resources available for research are finite, the return of aggregate research results necessarily requires the diversion of some resources away from the primary goals of research (producing generalizable knowledge for societal benefit). Justice requires balancing the interests of participants in receiving aggregate research results against allocating research resources in ways that might have greater benefits to society. For example, feeding back aggregate results to a large research population may require considerable time and preparation if they are to be comprehensively disclosed to a lay audience. Particularly if aggregate results have individual implications for participants, disclosing these results may be only the first step in managing them. This raises questions about appropriate disclosure and follow-up, and where necessary, incorporating research results into the participant's clinical care, including, if necessary, routine cognitive assessments. Relatedly, an increase in participants seeking clinical care in light of aggregate research results that they believe to be relevant to their individual health places a burden on the wider health system, and may deprive other patients who are entitled to care.

Conclusion

We have argued that the principles of respect for persons, beneficence/non-maleficence, and justice are not decisive with respect to an obligation to make aggregate research results available to participants in dementia research. Although there is no moral imperative to offer aggregate research results to participants in dementia research, neither is it the case that aggregate results should not routinely be made available to participants.

In fact, only about one-third of research participants receive any results from studies they have participated in.[48] This represents a potential missed opportunity to acknowledge and recognize the important contribution that participants have made to research, potentially satisfy their curiosity about the outcomes of the research, and to possibly engage participants in further research.

Thus, if the decision is made to offer aggregate results, it is important that the research protocol include specific information about what information will be shared, so that it can be reviewed both by the Research Ethics Committee and by participant representatives or community partners. It is important that the consent form indicate what, when, how, and to whom data will be disseminated, and provide sufficient detail for participants to make an informed choice about receiving results, as well as the option

to participate in the study without receiving aggregate results. It may be necessary for participants to go through a separate informed consent process at the conclusion of the study, prior to receiving aggregate results, to ensure that the participant has not changed their mind about receiving this information, and to give researchers an opportunity to inform them about new or unexpected information that was not conveyed during the initial informed consent process.

A clear strategy for communicating results should also be included as part of the research protocol, including what support will be provided to participants receiving research results.[49] Developing this communication strategy may require engaging with representatives of the research population, to identify their informational needs and preferences. For example, research suggests that participants prefer face-to-face communication when receiving feedback about research results, especially when findings relate to severe or untreatable conditions.

In summary, disclosing aggregate results of dementia research presents unique challenges. The principles of respect for autonomy, beneficence/non-maleficence, and justice require a nuanced interpretation in the context of fear of dementia. Despite near-consensus in the bioethics literature supporting the disclosure of aggregate research results, an investigator's decision not to provide aggregate results does not violate ethical requirements. Nevertheless, even in the absence of such an obligation, there may be good moral reasons to disclose aggregate results. In this regard, how we communicate results becomes particularly important. What we already know, what the results do (and do not) tell us, and what remains to be determined need to be part of a considered conversation with research participants.

Notes

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