Title:

Informing Cognitively Healthy Research Participants of Modifiable Dementia Risk Factors – Ethical Implications

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Abstract

Research has shown that up to 40% of dementia incidence can be accounted for by 12 modifiable lifestyle risk factors. However, the predictive value of these risks factors at an individual level remains uncertain. Ethical considerations of beneficence and non-maleficence, respect for autonomy, and justice —on which most ethical guidelines for disclosing individual research results are based— fail to provide conclusive justification for, or against, disclosing modifiable risk factors for future dementia to cognitively unimpaired research participants. We argue for a different approach to evaluating the disclosure of individual-level modifiable risk factors for Alzheimer's disease. Rather than focussing on individual-level disease prediction and prevention, we suggest that disclosure should be evaluated based on the impact of behavioural and lifestyle changes on current brain health.

1 Introduction

Dementia is a global epidemic that presents profound challenges to health care systems, families, and societies throughout the world. By 2050, the number of people living with dementia is expected to reach 139 million, and the associated costs to surpass $2.8 trillion by 2030 [1]. Evidence suggests that up to 40% of worldwide dementia can be accounted for by 12 modifiable lifestyle risk factors, many of which begin to impact in midlife, e.g., alcohol consumption, obesity, and hypertension, and which, therefore, could be prevented or reduced [2,3]. Pathophysiological processes underlying Alzheimer's Disease (AD), the most common form of dementia, are present decades before the onset of clinical symptoms [4].

The past decade has seen an exponential increase in focus on brain health, as a holistic state and set of processes that can be actively promoted through lifestyle choices [2,5]. Identifying the individuals at greatest risk for late-onset sporadic AD has been the focus of growing research efforts, in order to deliver targeted risk reduction and prevention interventions from midlife [6,7]. Recent studies of cognitively unimpaired middle-aged individuals show that modifiable risk factors for late-life AD, as assessed by measures like the Cardiovascular Risk Factors, Ageing and Dementia (CAIDE) risk score [8], are associated with worse cognition (e.g., poorer visual recognition [7], lower episodic and relational memory [9]) and declining brain structure (e.g., lower hippocampal volume [7]; thinner cortex, larger hippocampal fissure [10]), an estimated 23 years prior to dementia onset. (CAIDE scores identify individuals at increased risk for dementia based on a multifactorial assessment of several parameters, including age, years of education, systolic blood pressure, BMI, total cholesterol, and physical activity. CAIDE scores can also be calculated by including APOE ε4 carrier status.) Conversely, stimulating lifestyle activities are associated with better cognition (e.g., episodic and relational memory) in at-risk mid-life populations, and may protect against the

risk of sporadic late-onset AD, such as for those with a family history of dementia [11]. Another recent study found that inherited dementia risk (i.e., Apolipoprotein E [APOE] ε4 genotype) modulated the association between sex, lifestyle factors and cognition [9]. Whereas APOE ε4+ females showed a significant association between higher occupational attainment and stronger episodic and relational memory, APOE ε4- females did not. These findings suggest that modifiable lifestyle activities offset cognitive decrements due to inherited AD risk in mid-life and support the targeting of modifiable lifestyle activities for the prevention of Alzheimer's disease.

Studies like the ones described above often yield individual-level information about modifiable risk factors, in addition to group-level findings. Recent research shows that 9 out of 10 people want to know their risk of brain disease [12], and that once individuals know their personalized risk of AD, they adopt health behaviours faster [13]. Despite this, current clinical guidelines recommend against disclosing individual-level dementia risk to cognitively unimpaired individuals, due to the low predictive value of these risk factors for future dementia [14]. These recommendations against disclosure concern information about non-modifiable risk factors (e.g., APOE ε4 carrier status, amyloid-β in cerebrospinal fluid). By contrast, information about modifiable risk factors, (e.g., those captured in dementia risk scores like CAIDE) has not been discussed in previous recommendations regarding disclosure of dementia risk factors [14], despite recent studies showing that these factors are strongly associated with reduced brain health in mid-life [7,9,10].

Modifiable risk factors are critically different from non-modifiable factors, because they are actionable. Studies show that people want information more when they believe information will be useful in guiding their actions, and that actionability is the number one motive that drives people to seek health information [15]. Here, we argue that disclosing research-derived

modifiable risk information promotes current brain health, independent of its individual-level predictive value for future dementia, and thus, ought to be made available to research participants.

2 Current Ethical Guidance

Much of the current ethical guidance concerning the disclosure of individual research results has arisen in the context of genetics research. Historically, three criteria have been used to determine whether disclosure of individual research results is required: i) analytical validity (the results are scientifically valid and confirmed); ii) clinical significance (they have significant implications for a participant's health); iii) clinical 'actionability' (a course of action to ameliorate or change the clinical course of the disease is readily available) [16,17]. These criteria have typically been justified based on the so-called 'duty to warn', as well as the duty to avoid causing harm to research participants. Individual research results describing modifiable risk factors are unlikely to meet these conditions. While these results are scientifically valid, their predictive value at the individual level (i.e., the extent to which modifying a particular behavioural or lifestyle factor will reduce individual risk of dementia) remains uncertain. Moreover, the lack of established preventive or therapeutic interventions for AD dementia diminishes the requirement to make research results available (i.e., the clinical 'actionability' of the results) according to standard ethics guidelines.

Several commentators have argued that even when individual research results do not satisfy the above criteria, disclosure may nevertheless be permissible based on considerations of beneficence and non-maleficence, respect for participant autonomy, and justice. However, these same considerations have also been used to argue against disclosure. (For an overview of the debate, see [18]. As we argue below, considerations of beneficence and non-maleficence, respect for autonomy, and justice fail to provide a conclusive case in favour of,

or against, disclosing risk information about modifiable risk factors for dementia. However, if we reframe this information as concerning current brain health rather than future dementia risk, the case for disclosure is much more compelling.

3 Ethical Considerations Concerning Disclosure of Individual Research Results

3.1 Beneficence/Non-maleficence

Beneficence emphasises the importance of promoting and safeguarding the well-being of participants, while non-maleficence emphasizes the importance of minimizing possible harms to participants resulting from the conduct of research. The benefits of disclosing modifiable risk factors can be framed in terms of potential impact on dementia in later life [13]. Early and accurate information about modifiable risk may motivate participants to seek treatment for risk factors (e.g., for hypertension), adopt health behaviours faster, or seek further education and support services to help reduce their risk. However, as described above, the extent to which modifying behaviour or lifestyle factors will reduce individual-specific risk of dementia remains uncertain.

It can also be argued that disclosing modifiable risk factors to participants might have 'personal utility' [19], independently of an individual's dementia risk reduction. These benefits include arranging financial affairs, advance care planning, preparing family members, and altruistically enrolling in research. For example, knowledge of risk status might result in a participant altruistically enrolling in further research, from which they derive personal satisfaction independent of any health benefits. At the same time, some commentators have argued that the beneficence obligation of researchers (particularly non-clinician researchers), does not extend to offering results with personal utility [20].

A common concern relating to disclosure of dementia risk information to cognitively unimpaired individuals is psycho-social harm [21]. Studies have shown that for a significant portion of the population (26% - 39%), dementia is the most feared medical diagnosis, surpassing even cancer [22]. As a result, there is concern that risk disclosure can cause adverse psychological effects (e.g., anxiety, depression) [23,24]. Recent findings even show an increased risk of suicide attempt in individuals who received a recent diagnosis of mild cognitive impairment or dementia [25].

Yet, the disclosure of dementia risk, especially modifiable risk, is likely very different from a diagnosis of early dementia. This is supported by data showing that the risk of psychological harm from dementia risk disclosure is low, and that potential harm dissipates over time [13,19,23]. Research does suggest, however, that participant concerns about stigma or discrimination may be justified, and that the process of disclosing one's risk to others can be a significant source of anxiety [13].

Furthermore, studies have shown that knowledge of dementia risk can lead to altered perceptions or expectations about oneself (e.g., so-called 'hypervigilance'), which negatively influences performance (e.g., poorer performance on objective and self-assessment memory tasks), and can lead to avoidance of behaviours that protect against dementia (e.g., social integration) [26]. Finally, routine communication of risk may result in excessive testing and unnecessary treatment of age-related cognitive changes [27], which could impact on insurance or employment status, and resource allocation throughout the healthcare system.

3.2 Respect for Autonomy

A further consideration in favour of disclosing modifiable risk factors to participants is respect for autonomy, which calls for recognition of an individual's right to determine their own ends and values. By providing participants with information that they can incorporate into future decision-making, disclosing individual research results is argued to promote participant autonomy. Conversely, withholding information that might be used in decision-making —even with the aim of protecting participants from harm— may violate autonomy because it interferes with a participant's self-determination [28], particularly when individuals request research results.

Conversely, some have argued that disclosing information about dementia risk does not promote participant autonomy. Insofar as these risk factors lack predictive value, they do not convey any meaningful information on which to base future decision-making [24]. Moreover, if participants misinterpret these results (i.e., if participant form false beliefs about their level of risk), disclosing them potentially undermines their ability to act according to their values. While the empirical literature on feeding back dementia risk information to cognitively unimpaired participants is limited, there is evidence that participants can understand the prognostic uncertainty of inherited dementia risk [13]. This argues against a default assumption that participants will misinterpret risk information, or that they are incapable of incorporating information of limited predictive value into their decision-making rationally, especially if adequate support and guidance is provided.

3.3 Justice

While typically receiving less attention than considerations of beneficence and respect for autonomy, the feedback of individual research results does raise considerations about justice.

Justice requires that there should be fairness in the distribution of the benefits and burdens of research. With respect to disclosing individual research results, this requires that results are made available in a consistent way. The fact that certain individuals or groups may be more difficult to engage, or require greater resources (e.g., follow-up) to ensure their understanding of results, is not an acceptable basis for withholding results. An obvious obstacle here is cost: larger research studies may simply have more resources available for follow-up than smaller studies, meaning that participants in a study with a larger budget may be more likely to receive the same results than those participating in a smaller study.

4 Focus on Optimizing Current Brain Health

As the above discussion demonstrates, considerations of beneficence and non-maleficence, respect for autonomy, and justice do not provide conclusive justification for, or against, disclosing risk information, including modifiable risk, for future dementia to cognitively unimpaired research participants.

Therefore, we argue for a different approach to evaluating the disclosure of individual-level modifiable risk factors for Alzheimer's disease. Rather than focussing on individual-level disease prediction and prevention, we suggest that disclosure should be evaluated based on the impact of behavioural and lifestyle changes on current brain health. Even if a middle-aged individual who shows high modifiable risk of AD (e.g., based on aggregate dementia risk scores, such as the CAIDE score excluding of APOE status, or scores of lifestyle activities, such as the Lifetime of Experiences Questionnaire, that may indicate social isolation, physical inactivity and lack of intellectual stimulation) never develops dementia, they can benefit from adapting a healthier lifestyle in the present. For example, research has found that more frequent engagement in physically, socially and intellectually stimulating activities is associated with stronger episodic and relational memory in mid-life individuals with a family

history of dementia [11], and higher educational attainment is associated with episodic and relational memory in females who carried the APOE ε4 allele [9].

By focusing on the impact of modifiable lifestyle factors on current brain health, a clear argument emerges that disclosure is consistent with beneficence, respect for participant autonomy, and justice. The benefits of disclosure are not contingent on a reduction in dementia risk (which is itself contingent on whether the participant would have gone on to develop dementia at all), and the likelihood of psychosocial harms is mitigated by the fact that individual research results are not framed in terms of the risk of developing dementia. Moreover, because these results are not intended to be predictive of future disease, they convey meaningful information on which a participant can base decision-making about their brain health. And because they are reasonably simple to convey, additional costs associated with feedback are not likely to restrict feedback only to large studies. Indeed, this might provide certain groups access to information they wouldn't otherwise receive; insofar as this is an enticement to participate, this might help to attract otherwise underserved participants to research.

Focussing on the impact of risk disclosure on brain health is also consistent with a more participant-centric model of research. Providing individual-level results acknowledges a participant's contribution to research and has been argued to improve transparency and trust in the research enterprise [18], which in turn might lead to increased enrolment and retention of long-term relationships with research participants. This approach is particularly valuable for establishing more inclusive research with underrepresented groups, for whom relationships of trust with the biomedical community are currently lacking.

When individual research results are returned, the process of communicating them to participants must strive to promote understanding of the meaning, application, and limitations

of this information. This requires training of staff on how to deliver this feedback so that the information is given in a standard and accurate way. Studies show that individuals vary greatly in extent to which they desire health information [29]. Therefore, a transparent strategy for communicating results, e.g., via prior discussion during the study consent process, should be part of the research protocol, including what support and guidance will be provided to participants. Participants may need to go through a separate informed consent at study conclusion, prior to receiving results, to ensure that they have not changed their mind about disclosure, and to inform them about new or unexpected findings that were not discussed in the initial informed consent.

5 Conclusion

When viewed from the perspective of dementia risk, the benefits of receiving individual-level research results are indeterminate, making it difficult to assess whether disclosure of risk information is ethically permissible. We argue that focussing on the impact of disclosure on current brain health, rather than risk of future dementia, is clearly supported by considerations of beneficence non-maleficence, respect for autonomy, and justice.

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Declaration of Interest

The authors declare no conflicts of interest.

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