Genetic predisposition and modifiable risks for late-life dementia

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Dementia is a syndrome of cognitive and functional impairment. Although age remains the primary risk factor, several other diverse risk factors have been linked with dementia, including genetic factors such as the presence of the ApoE4 allele, and lifestyle factors including smoking and exercise. With ever-ageing populations, interventions that offer some prospect of dementia prevention are being scrutinized. A critical issue is how the genetic and lifestyle factors interact; that is whether the genetic risk for dementia be modified by a healthy lifestyle In this issue, Licher *et al* find that modifiable lifestyle risk factors were only able to reduce dementia risk in people with low genetic risk. This is in contrast to previous studies which have shown that lifestyle is able to mitigate the effects of genetic risk on the development of dementia.

Licher *et al* carry out a large, population-based cohort of over 6300 people aged 55+ in Rotterdam, in which they examined dementia incidence over 15 years. Participants were 69 years old on average, mostly women (56.2%), 27.5% had high genetic risk, the majority were classified as having a favorable lifestyle profile (65.3%), and 14.4% (n=915) developed dementia in the follow-up period. The modifiable factors that the authors examined included regular physical activity, healthy diet adherence, avoiding social isolation, not smoking, and being free from diabetes or depression and were graded as being of either low, intermediate or high risk. Genetic risk, estimated from ApoE allelic variation and a polygenic risk score with 27 other genetic variants, was graded likewise. The authors key finding is that modifiable lifestyle risk factors were only able to reduce dementia risk in people who did not have an ApoE4 allele and hence were at lower genetic risk.

The Licher *et al* study findings contrast with those from another large, population-based study using data from the UK Biobank including 196,383 individuals (2). Healthy lifestyle was quantified similarly to the Rotterdam study (a self-report composite of smoking status, alcohol consumption, dietary patters, and physical activity). In the UK Biobank, the polygenic risk score (an index of several different genes that were associated with dementia) included more genetic variants, and was analyzed differently (though this may limit generalizability). Neither study is a clinical trial, but in contrast to the Rotterdam study, UK Biobank suggests that the genetic and lifestyle associations are independent and additive. That is, modifiable lifestyle factors impacted dementia risk regardless of genetic risk (Figure 1).

Both Rotterdam and UK Biobank are careful, expensive, established, prospective studies meant to better understand adult disease. They differ in sample size and the proportion of incident cases. Of 6352 studied in Rotterdam, 14.4.% had developed dementia at 15 year follow-up (median 14.1 years), whereas only 0.9% of the UK Biobank's sample of 196,383 developed dementia at a median of 8.0 years). Not by coincidence, the studies also differ in how cases were ascertained. Rotterdam is population-representative, and employs for-purpose, research-grade diagnoses. This is a considerable undertaking. UK Biobank is costly too, but has focused its larger budget on a much larger sample size, with investment in 'omics profiling, and with disease defined through linkage to health care records. Both studies confirm that ApoE4 (and to some extent, high polygenic risk scores) do indeed increase the risk of dementia. The studies differ in how both the polygenic risk scores and mitigating factors were measured, and in samples size, case ascertainment, and diagnostic tools. They will inform meta-analyses, which presumably are already under way, and likely to include other recent studies that support an impact of lifestyle factors that are somewhat robust to genetic risk (3,4).

Meta-analysis of these and other observational studies is one way to better understand whether genetic risk for dementia can be modified by a healthy lifestyle. Clinical trials are another, but despite their high

standing in the evidence hierarchy, in practice they often exclude people most at risk **[AU: is this particularly true in dementia?]**(5). The Rotterdam and UK Biobank studies tell us that however we proceed, we must better understand outcomes in those most at risk - and not just using genetic factors. We might begin by recognizing that ageing is essential, rather than incidental, to dementia disease expression. This obliges a focus on people living with frailty – who most often are not just excluded in dementia trials but also at higher risk. For example, a frailty index of age-related health deficits was associated with increased rates of dementia, even with known dementia risk factors as covariates (6), and moderated the expression of neuropathological lesions associated with late-life Alzheimer disease (7). Might frailty also moderate the relationship between genetic risks and dementia expression? If so, further questions will need to be addressed. Is the effect of frailty on the relationship between genes and dementia intrinsic or indifferent to overall health? Does a healthy lifestyle reduce the clinical expression of neuropathology in the face of many age-related deficits?

Another approach is to understand how dementia arises. For many people, dementia is related to the dynamic changes in cognition seen as they develop and recover from acute illness. Estimates suggest that acute encephalopathy, or delirium - is associated with an increased risk of dementia (8). In this condition older adults that are too frail are at a greater risk than less frail adults (9). As a consequence, older adults who develop delirium may represent an ideal target group both for natural history studies and large clinical trials. We know that not everyone who has delirium recovers (10). As with age-related health deficits, delirium impacts how the neuropathological lesions of dementia are expressed (11). Less well appreciated is that although some with delirium develop dementia others improve with persisting cognitive impairment that does not meet dementia criteria (8). In short, “prevented dementia” might not be the same as having no cognitive impairment, whether or not such impairment meets dementia criteria. Further, we still do not know whether individuals with delirium that do not recover would otherwise have developed dementia or if that disease is a separate entity. If the latter, it will require new biomarkers, including neuropathological ones. Given how common dementia is soon forecast to be (12), and how much we will need not to miss means of at least reducing its impact, this is one example where the need for deep phenotyping will be both acute and severe.

Reducing the extent of disease expression in people prone to develop dementia in late life is a tricky business. Studies that investigate whether dementia can be prevented at all such as that here, and then whether it can be prevented in those at greatest risk, can be commended for their clear-eyed approach.

Figure legend: A representation of the Rotterdam study sample (n=4153) who had the most favorable lifestyle risk profile, stratified by genetic risk. Each person represents 100 participants. The red persons indicate the proportion of the total sample with dementia.

[AU: since it might not be a complete direct equivalency to compare the two studies here, I recommend that only the Rotterdam study is included in the figure]

References:

1. Licher S, Ahamd S, Karamujic-Comic H, Voortman T, Leening MJG, Ikram MA, Ikram MK. Genetic predisposition, modifiable risk factor profile and 34 long-term dementia risk in the general population Nature Med This issue.
2. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, Llewellyn DJ. Association of Lifestyle and Genetic Risk With Incidence of Dementia. JAMA. 2019 Jul 14. doi: 10.1001/jama.2019.9879. PMID: 31302669.
3. Lyall DM, Celis-Morales C, Lyall LM, Graham C, Graham N, Mackay DF, Strawbridge RJ, Ward J, Gill JMR, Sattar N, Cavanagh J, Smith DJ, Pell JP. Assessing for interaction between APOE ε4, sex, and lifestyle on cognitive abilities. Neurology. 2019 Jun 4;92(23):e2691-e2698.
4. Dekhtyar S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of dementia mitigated by cognitive reserve: A cohort study. Ann Neurol. 2019 Jul;86(1):68-78. doi: 10.1002/ana.25501.
5. Canevelli M, Trebbastoni A, Quarata F, D'Antonio F, Cesari M, de Lena C, Bruno G. External validity of randomized controlled trials on Alzheimer's Disease: The biases of frailty and biological aging. Front Neurol. 2017 Nov 27;8:628. doi:10.3389/fneur.2017.00628. PMID: 29230192.
6. Rogers NT, Steptoe A, Cadar D. Frailty is an independent predictor of incident dementia: Evidence from the English Longitudinal Study of Ageing. Sci Rep. 2017 Nov 16;7(1):15746. doi: 10.1038/s41598-017-16104-y. PMID: 29146957
7. Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. Lancet Neurol. 2019 Feb;18(2):177-184. doi: 10.1016/S1474-4422(18)30371-5. Erratum in: Lancet Neurol. 2019 Mar;18(3):e2. PubMed PMID: 30663607.
8. MacLullich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long term cognitive impairment. Int Rev Psychiatry. 2009 Feb;21(1):30-42. doi: 10.1080/09540260802675031.
9. Persico I, Cesari M, Morandi A, Haas J, Mazzola P, Zambon A, Annoni G, Bellelli G. Frailty and Delirium in Older Adults: A Systematic Review and Meta-Analysis of the Literature. J Am Geriatr Soc. 2018 Oct;66(10):2022-2030.doi: 10.1111/jgs.15503. PMID: 30238970.
10. Adamis D, Devaney A, Shanahan E, McCarthy G, Meagher D. Defining 'recovery' for delirium research: a systematic review. Age Ageing. 2015;44(2):318-21. doi: 10.1093/ageing/afu152. PMID: 25476590.
11. Davis DH, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG, Matthews FE, Cunningham C, Ely EW, MacLullich AM, Brayne C; Epidemiological Clinicopathological Studies in Europe (EClipSE) Collaborative Members. Association of delirium with cognitive decline in late life: A neuropathologic study of 3 Population-Based Cohort Studies. JAMA Psychiatry. 2017;74(3):244-251. doi: 10.1001/jamapsychiatry.2016.3423. PMID: 28114436.
12. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al., Dementia prevention, intervention, and care. Lancet. 2017 Dec 16;390(10113):2673-2734. doi: 10.1016/S0140-6736(17)31363-6. PMID: 28735855.

Disclosures

In addition to academic and hospital appointments, Kenneth Rockwood is President and Chief Science Officer of DGI Clinical, which in the last five years has contracts with pharma and device manufacturers (Baxter, Baxalta, Biogen, Shire, Hollister, Nutricia, Roche, Otsuka) on individualized outcome measurement. In 2017 he attended an advisory board meeting with Lundbeck. Otherwise any personal fees are for invited guest lectures, rounds and academic symposia, received directly from event organizers, for presentations on frailty. He is Associate Director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research (CAN-137794), with additional funding from the Alzheimer Society of Canada and several other charities, as well as from Pfizer Canada and Sanofi Canada (in Phase 1, 2014-2019). He receives career support from the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research, and research support through grants from the Canadian Institutes of Health Research, the Canadian Frailty Network, the Nova Scotia Health Research Foundation, the Nova Scotia Health Authority Research Fund and the Fountain Family Innovation Fund of the QEII Health Science Centre Foundation.