Neurobiology of Aging 76 (2019) 217–218

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Letter to the Editor

Genetic influence of plasma homocysteine on Alzheimer's disease

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Nomenclature

tHcy	total homocysteine
SNP	single-nucleotide polymorphism
MR	Mendelian randomization

Two interesting papers (Roostaei et al., 2017; van Meurs et al., 2013) have appeared recently concerning associations of plasma total homocysteine (tHcy) with diseases, including one (Roostaei et al., 2017) in Neurobiology of Aging. Although their results are valuable, there is a risk of misinterpretation.

Both reports based their analyses on genetic scores that explained at most 6% of the variance in tHcy, as the earlier report (van Meurs et al., 2013) acknowledged, although we note that all single-nucleotide polymorphisms (SNPs) included in their model were highly significant. Roostaei et al.'s genetic score used 13 of the 18 SNPs in van Meurs et al.'s score. Concerning the low proportion of tHcy variation explained, Roostaei et al. pointed out that nevertheless the statistical power of their sample size of 54,000 people (>80% to detect odds ratios larger than 1.12 for the effect of Hcy on Alzheimer's disease [AD] risk) would be sufficient to achieve significant results from their genetic score. This figure is similar to the one reported by van Meurs et al. (>85% power to detect an 11% increased risk). Thus, both studies seemingly had sufficient statistical power to establish risks with a usual magnitude in AD studies. However, the fact remains that their conclusions, that is, of no causal association of raised plasma tHcy with coronary artery disease (van Meurs et al., 2013) or with AD (Roostaei et al., 2017), were based on genetic scores with limited predictive ability.

In van Meurs et al.'s Table 1, the model's parameter estimates showed that 8 of the 18 SNPs were associated with lower levels of tHcy, yielding a total additive effect for the 18 SNPs of 0.109 standard deviations of tHcy in a standard normal scale, which is a small shift in the normalized distribution. This shift is unlikely to be clinically significant.

There are likely to be many other SNPs that influence plasma tHcy because its heritability is believed to be substantial. Estimates for the genetic contribution/heritability of plasma homocysteine range from 27% to 63% (Bathum et al., 2007; Siva et al., 2007), depending on age (Bathum et al., 2007). There are also many nongenetic factors, such as B vitamin levels (Refsum et al., 2006), that affect plasma tHcy. Serum folate alone has been suggested to account for 10% of the variance (Siva et al., 2007). None of these other factors, genetic or nongenetic, were taken into account in either study.

Another problem is that the relevance of each SNP depends on the phenotypic expression of its genotypes. For instance, the effect of *MTHFR* rs180113 is mainly seen at low folate status (Refsum et al., 2006), which hardly exists in countries such as the United States with folic acid fortification. This raises some doubt as to whether the reported SNPs actually explained the stated proportion of tHcy variance.

Both studies used Mendelian randomization (MR), which is an excellent method to attribute causal effects to observational associations avoiding confounding or reverse causation, provided the conditions for its use are fulfilled (Bochud et al., 2008; Ebrahim and Davey Smith, 2008). As van Meurs et al. state, MR is based on genes of known function. It is most unlikely that the functions of all 13 genes used to compute the genetic scores of each study are fully known. MR further requires that suitable variants are available, which assumes that their effects are known. Present knowledge of the genetics of AD (Roostaei et al., 2017) and of coronary artery disease (van Meurs et al., 2013) does not justify that assumption. Pleiotropy can lead to erroneous inferences using MR, particularly leading to biased estimates of the causal effect and to increased type I error probabilities (Bowden et al., 2015). We are learning that even certain much-studied genes, for example, *APOE*, are pleiotropic. Several of the genes used in these two studies and their variants are known to be pleiotropic, for example, *MTHFR* (Jennings and Willis, 2015) and *MTR* (Karaca et al., 2016). Indeed, van Meurs et al. mentioned the pleiotropic roles of the relevant *HNF1A* variant. These and other limitations and necessary conditions for correctly applying MR are given, respectively, in Table 5 of Ebrahim and Davey Smith (2008) and Table 1 of Bochud et al. (2008); listed limitations include, for instance, pleiotropy and the lack of suitable variants.

In conclusion, the results of these two studies need to be interpreted with care. First, the probably inappropriate use of MR in each study does not justify the major conclusions that have been drawn about the roles of tHcy in the causation of coronary artery disease (van Meurs et al., 2013) and of AD (Roostaei et al., 2017). In addition, the models' seemingly low proportion of explained variance of plasma tHcy (<6%) indicates a limited predictive ability, regardless of the size of the effect implied by this figure and both studies' large sample sizes. In particular, we suggest that your readers should be cautious about accepting the conclusion of Roostaei et al. that there is no causal association between elevated Hcy and AD in people of European ancestry, without considering the large body of observational evidence that is consistent with such an association, as

DOI of original article: 10.1016/j.neurobiolaging.2017.09.033.

recently reviewed (McCaddon and Miller, 2015; Smith et al., 2016), or the results of a clinical trial (Douaud et al., 2013). We conclude that the negative genetic result of Roostaei et al. should direct attention to the many nongenetic factors that determine tHcy, which may be amenable to modification and so could be used to influence cognitive decline (Smith et al., 2018).

Disclosure

The authors have no conflicts of interest.

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https://doi.org/10.1016/j.neurobiolaging.2018.08.028

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