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INVITED EDITORIAL

Understanding family history of heart disease: a (good) patient interview vs. genetics

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This editorial refers to 'Genetic and Clinical Factors Underlying a Self-Reported Family History of Heart Disease', by A. Jowell *et al*. https://doi.org/10.1093/eurjpc/zwad096.

> 'One should pay attention to the first day the patient felt weak; one should inquire why and when it began. These are the key points to keep in mind. After these questions have been cautiously considered, one should ask the patient how his head feels, or if he has any pain or if he feels heavy.. In regard to the chest, one should ask the patient if he has pain there and if he has a slight cough, with pain in the abdomen when he coughs.'
>
> Littre's Translation of Hippocrates, 2, 436-40: Regimen in Acute Disease

Patient interview about symptoms and individual clinical history is a principle of Hippocratic medicine, still representing a cornerstone of clinicians' routine activity. The inquiry on personal lifestyle (including diet, smoking status, exercise, etc.), on past medical history, and, importantly, on disease family history is the first step in the planning of the diagnostic and therapeutic path. One may argue that the availability of novel sophisticated tools for individual risk stratification and decision-making, based on circulating biomarkers, multi-modal imaging, invasive diagnostics, and, possibly, on the assessment of individual genetic characteristics, may limit the relevance of searching for family history of diseases in contemporary medicine. In the present issue of the journal, Jowell *et al.*[1] have explored at which extent family history of heart disease (FHHD) can be explained by common clinical biomarkers, a polygenic risk score for coronary artery disease (PRS_{CAD}) and by the heterozygous familial hypercholesterolemia (HeFH) genotype. They have performed a cross-sectional analysis on 166 714 United Kingdom Biobank participants without pre-existing coronary artery disease (CAD) using a self-reported FHHD as outcome, and several clinical features as exposures (diabetes, hypertension, smoking, apolipoprotein B-to-apolipoprotein AI ratio, waist-to-hip ratio, high sensitivity C-reactive protein, lipoprotein(a), and triglycerides) and genetic risk markers (PRS_{CAD} and HeFH). At population attributable risk analysis, the authors report that only 21.9% of the risk of reporting a FHHD may be attributable to clinical factors, 22.2% to genetic factors and 36.0% to their combination. With the recent development and diffusion of high-yielding genetic tools and the integration of novel biomolecular and bioinformatic technologies, the use of polygenic scores for risk stratification is ready to translate from bench to bedside. The use of these scores, alongside to the traditional assessment of well-known monogenic diseases and clinical risk factors, may hence help risk stratification and drive the implementation of lifestyle interventions and therapeutic strategies in risky populations to prevent incident cardiovascular events.

Nonetheless, the contribution of either environmental or genetic factors to FHHD remains largely unexplained: many other factors, which have been disregarded in the present work, may indeed explain FHHD. Causal contribution to FHHD of a variety of non-genetic determinants is likely and should not be overlooked (such as socioeconomical status, environmental exposures—air and water pollutants, food contaminants, chemicals, radiations, etc.—environmental stress, and personality traits).[2,3] This may raise a claim for an extension of the clinical interview to all these items. Moreover, there is evidence that epigenetic modifications can be influenced by exogenous stimuli and can be transferred to next generations, thus potentially contributing to the inheritance of a susceptibility to disease.[4]

Relevant observation from the present paper also comes from the analysis of the incidence of CAD and of PRS_{CAD} for an increasing number of relatives with history of heart disease. There is indeed a marked difference in the incidence of CAD among enrolled individuals, according to the number of affected family members (4.7% among subjects with no family member vs. 13.2% among subjects with 3 family members). A similar increase was reported in the percentile of PRS_{CAD} (47%: no family members vs. 61%: 3 family members), thus suggesting that genetic background may indeed represent a proxy for the effective individual risk.

Although of potential clinical relevance, we should be cautious with the conclusions of the study by Jowell. One of the most important limitations is related to the assessment of family history: what 'heart disease' is, exactly, in a patient's mind? There is evidence that the accuracy of self-reported family history of cardiovascular risk factors as diabetes and arterial hypertension may be significantly influenced by the accuracy of self-reported personal health status of relatives.[5] Moreover, a simple enquiry may miss a significant proportion of individuals with positive FHHD, as compared to a detailed questionnaire, thus possibly leading to an incorrect classification of familial risk.[6]

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Further, heart disease is not fully equivalent to ischaemic heart disease or CAD. The expositions considered by the authors for the aims of the present study are mainly related to CAD, rather than to the whole spectrum of heart diseases (including cardiomyopathies, valve disease, pericardial disease…).

It is likely that the global probability of a patient to report FHHD may be difficultly identified in the clinical practice, up-to-date. Nevertheless, soon, the implementation of artificial intelligence to big data analysis, crossing information deriving from different sources as genetic databases, healthcare systems, public administrations, and environmental studies, may overcome such difficulties and provide a more accurate estimate of the global heritable burden of risk for cardiovascular diseases. Such technologies are also expected to identify novel risk factors, meant as currently unrecognized genetic, clinical, and environmental factors, and improve their management through personalized approach, to reduce the burden of cardiovascular events in the next generations.

Until then, as confirmed by Jowell *et al*., the clinical assessment of FHHD remains an unparalleled cornerstone in patient assessment and risk stratification.

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Data availability

No original data are reported.

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