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Perspective

Quantifying the Importance of Interleukin-6 for Coronary Heart Disease

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For many years it was widely believed that known vascular risk factors could explain only about half of all cardiovascular disease [1], leaving much to be discovered about other causes of stroke and heart attack. There has been considerable interest in the possible aetiological role of inflammation in vascular disease. Interleukin-6 (IL-6) is one of a number of inflammatory markers that have been studied [2]. There are, however, substantial and often unrecognised challenges to quantifying the full effects of risk factors such as IL-6.

A particular problem in establishing the true nature of the association between exposures and outcomes arises from the difficulty of achieving a good estimate of the true level of the risk factor of interest. It is very difficult to establish an individual's usual level of exposure to an inflammatory marker such as IL-6, because it has a short half life and is complex to assay. The same challenge also applies to well-established, and apparently easier to measure, determinants of risk such as blood pressure and cholesterol because they also fluctuate substantially over relatively short time periods [3]. Therefore a key strength of a new study by John Danesh and colleagues, reported in this issue of *PLoS Medicine* [4], is the substantial effort undertaken to overcome this problem and obtain reliable estimates of the association between IL-6 and coronary heart disease [5]. Whether the findings for IL-6 provide substantial new insight into the causation of cardiovascular disease is, however, rather less clear.

The New Study

Danesh and colleagues present new data on IL-6 levels from two population-based prospective cohorts, the Reykjavik Study and the British Regional Heart Study (BRHS), which together involve 24,230 mostly middle-aged individuals with an average of almost 20 years of follow-up per participant [5]. After excluding participants with any evidence of baseline cardiovascular disease, 2,138 incident cases of coronary heart disease (CHD) were available for analysis. The researchers evaluated associations between long-term circulating IL-6 levels and CHD risk in these two population-based cohorts. They then used findings from these two new studies to update a systematic review of all prospective, population-based studies on IL-6 and CHD published before May 2007.

Controlling for Imprecise Measurement of IL-6

In epidemiological studies, imprecise measurement of an exposure of interest leads to underestimation of the strength of the association with the outcome [5]. The bias caused by random error in measuring exposure was first highlighted in the 1990s in reports relating blood pressure levels to vascular risk, in which imprecise measurement of blood pressure was shown to substantially underestimate the strength of the association with both stroke and heart attack [3].

Since those first reports, a number of approaches have been developed to control for "regression dilution bias" [6]. The associations of IL-6 with coronary heart disease reported by Danesh and colleagues were adjusted using an established technique based upon repeated assays of IL-6 done several years apart in a sample of participants. Adjustments for errors in exposure measurement were also made for the covariates included in the multivariable models fitted to the data from the Reykjavik and BRHS studies, providing for uniquely powerful adjustment of potential confounders of the association of IL-6 with CHD. As such, the results provide a particularly reliable estimate of the strength of the association of IL-6 with CHD and establish a standard against which future studies of association might be judged.

New Evidence about the Effects of IL-6

The association of IL-6 with the risk of CHD was found to be similar in nature and magnitude to that of a number

Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, et al. (2008) Long-term interleukin-6 levels and subsequent risk of coronary heart disease: Two new prospective studies and a systematic review. PLoS Med 5(4): e78. doi:10.1371/journal.pmed.0050078

John Danesh and colleagues show that long-term IL-6 levels are associated with coronary heart disease risk, thus highlighting the potential relevance of IL-6–mediated pathways to coronary heart disease.

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Abbreviations: BRHS, British Regional Heart Study; CHD, coronary heart disease; IL-6, interleukin-6

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of major established determinants of vascular disease. The comparability of the findings of the Reykjavik study to those of the BRHS study provides reassurance that these findings are unlikely to be simply the result of chance. Likewise, when viewed in the context of the 15 other studies of IL-6 included in the meta-analysis, there was striking similarity in the direction of association across the different studies. There was some variability between studies in the magnitude of the associations observed that is not explained by Danesh and colleagues' exploratory analyses. However, the analytic options available to explore heterogeneity in the strength of association are limited, and the meta-regression technique used by Danesh and colleagues would not have provided great power to detect effects of study level characteristics. It therefore remains possible that variation in the techniques used for the collection, storage, and analysis of the blood samples on which the IL-6 assays were done could have influenced differently the magnitude of association identified in each of the contributing studies.

In addition to the association with CHD, IL-6 levels were also strongly associated with a number of established risk factors and other inflammatory markers. For example, there were moderate associations of IL-6 with smoking, diabetes, and dyslipidaemia. Accordingly the strength of the association between IL-6 and CHD varied between models including different sets of covariates and was attenuated when covariates strongly correlated with IL-6 were included. While the position of IL-6 in the causal pathway of some of the covariates included in the models is reasonably well understood, the pathophysiological relationship with other of the established determinants of vascular risk is less clear. The extent to which IL-6 might account for previously unexplained vascular risk cannot be quantified from these data. However, it seems unlikely that IL-6 makes a major contribution to vascular disease causation that is completely independent of the many other risk factors already identified.

Clinical Implications

While impressive in their rigour, the findings from this study are probably rather limited in regard to their clinical implications. Future studies of interventions for the control of vascular disease might gain insight into mechanisms of action through assay of IL-6. Likewise, IL-6 could be a target for the development of new chemical entities designed to modify vascular disease progression.

There are, however, almost certainly better foci of attention than IL-6 for physicians, researchers, and policy makers seeking to reduce the huge global burden of vascular disease [7]. It is now widely accepted that 90% or more of vascular disease can be explained on the basis of known risk factors, so these new data about IL-6 probably have relatively little to add in terms of our understanding of causation [8]. There are also multiple interventions that modify these known risks and avert premature death and disability from vascular disease at low cost. Therefore there is little need for a new and probably costly drug that acts via IL-6. The better application of proven risk stratification methods and the more efficient delivery of proven management strategies could already cut a swathe through the current vascular disease burden [9]. These proven strategies should remain the priority, particularly in developing regions of the world where most vascular disease now occurs. A focus on the identification of practical strategies for the delivery of existing interventions could deliver hugely cost-effective global health gains [10]. ■

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