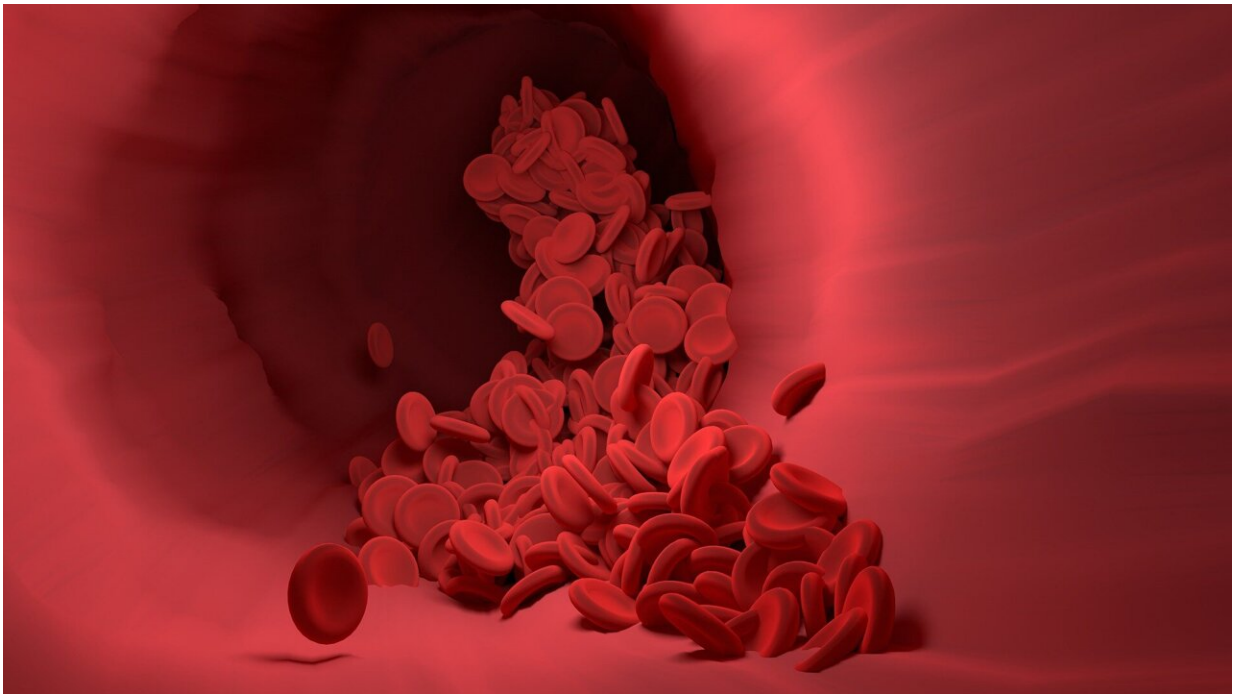# Novel AI algorithm could help personalize the prevention of cardiovascular disease

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A novel artificial intelligence (AI) algorithm accurately estimates the risk of heart disease caused by cumulative exposure to cholesterol and blood pressure levels and the benefits of lowering both—thus providing the essential information needed to make individual treatment decisions. The late breaking research was presented in a Hot Line session on 28 August at ESC Congress 2022.

"This study shows for the first time how to embed the causal effects of low-density lipoprotein (LDL) cholesterol and systolic blood pressure (SBP) into AI algorithms," said principal investigator Professor Brian Ference of the University of Cambridge, U.K. "These algorithms could be used to inform decisions for individual patients on the optimal timing, intensity and duration of LDL and SBP lowering to most effectively prevent atherosclerotic cardiovascular events."

Atherosclerotic cardiovascular disease is a chronic progressive disease that begins early in life and slowly progresses over time. Randomized trials have demonstrated that lowering LDL and SBP reduces the risk of atherosclerotic cardiovascular events. However, Mendelian randomization studies show that lifelong exposure to lower LDL and SBP is associated with much larger reductions in the risk of cardiovascular events compared to the reductions observed in randomized trials from lowering LDL and SBP starting later in life. This suggests that lowering LDL and SBP earlier in life may substantially improve the prevention of cardiovascular disease. However, the optimal timing, duration and intensity of LDL and SBP lowering to prevent cardiovascular events is unknown.

Clinicians use risk estimating algorithms to select persons with an elevated likelihood of heart disease who may benefit from therapy. However, these algorithms do not include the effects of LDL and SBP observed in randomized trials or Mendelian randomization studies and thus may not capture the true benefit of lowering LDL or SBP. Therefore, the objectives of this study were twofold. First, to evaluate whether current risk scores accurately estimate the baseline risk of cardiovascular events caused by LDL and SBP and the benefit of lowering LDL and SBP beginning at any age and extending for any duration. Second, to evaluate, using an AI algorithm, whether adding the causal effects of LDL and SBP more accurately estimates cardiovascular risk and benefit.

The Causal AI algorithm was used to estimate the effects of LDL and SBP in discrete time units of exposure (conditional on previous exposure to reflect the biology of how atherosclerosis develops) among 1.8 million individuals, including 1,320,974 enrolled in Mendelian randomization studies evaluating 140 variants associated with LDL and 202 variants associated with SBP, and 527,512 participants enrolled in 76 randomized trials evaluating LDL or SBP lowering therapies.

The accuracy of the Joint British Societies' (JBS3) algorithm was evaluated, both alone and after adding Causal AI effects of LDL and SBP in: 1) an independent sample of 445,771 participants in the U.K. Biobank to assess how well these algorithms estimated lifetime risk and benefit; and 2) 48,315 participants in LDL and SBP lowering trials to assess how well these algorithms estimated the short-term benefit of lowering LDL, SBP or both observed in the trials. The primary outcome was major coronary events (MCE), defined as the first occurrence of a fatal or nonfatal myocardial infarction, or coronary revascularization. The secondary outcome was major cardiovascular events (MCVE), defined as the first occurrence of a major coronary event or nonfatal ischemic stroke.

The study had three main findings. One, the JBS3 algorithm systematically underestimated the risk of MCE among persons with lifelong higher LDL, SBP or both; and systematically overestimated risk among those with lifelong exposure to lower LDL, SBP or both.

Professor Ference said, "This finding explains why current risk algorithms lead to the biologically implausible conclusion that LDL and SBP—the two main modifiable causes of atherosclerotic cardiovascular events—do not meaningfully contribute to the risk of cardiovascular events. By contrast, including the causal effects of LDL and SBP, derived from the Causal AI algorithm, accurately estimated the risk of MCE at all ages among persons with both higher and lower lifetime

exposure to LDL, SBP or both."

Two, the JBS3 algorithm systematically underestimated the benefit of maintaining lifelong lower LDL, SBP, or both on MCE. In contrast, including the causal effects of LDL and SBP accurately estimated the benefit of maintaining lifelong lower LDL and SBP at all ages. Three, the JBS3 algorithm systematically underestimated the benefit of lowering LDL, SBP or both starting later in life as compared to randomized trials of LDL and SBP lowering therapies. By contrast, including the causal effects of LDL and SBP accurately estimated the benefit of lowering LDL, SBP, or both starting later in life during every month of follow-up observed in randomized trials.

Professor Ference said, "Current risk estimating algorithms are biased against prevention because they systematically underestimate the benefit of lowering LDL and SBP. This may lead to the false conclusion that waiting to lower LDL and SBP until later in life is more effective and costs less than lowering LDL and SBP at a younger age. Replacing these algorithms with Causal AI has the potential to personalize the prevention of cardiovascular disease and illustrate the public health and economic value of investing in cardiovascular prevention."

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