COMMENTARY

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The earliest history of human atherosclerosis

Atherosclerosis is not a modern disease. Currently, it is the number one cause of death in the 21st century and is associated with our current rich diet and low levels of exercise. However, archaeological and paleopathological studies have demonstrated that atherosclerosis has existed in humans for thousands of years. Allam et al in the HORUS study used CT (computed tomography) to examine mummified bodies from multiple ancient civilizations: Egypt (3100 BCE), Peru (1500 BCE), early Southwestern USA Puebloans (1000 AD) and hunter-gatherers from the Aleutian Islands (1500 AD).[1−4] These studies clearly demonstrated arterial calcifications typical of atherosclerosis in 30%-40% of the mummies that were examined. Thus, atherosclerosis has been a part of human history for thousands of years even in pre-agrarian and pre-industrial societies. Of course, some of these ancient individuals, for example, Egyptian pharaohs and nobility, lived an elite lifestyle and consumed a very rich diet. However, other mummies from laborers and non-elite members of society also demonstrated clear evidence of atherosclerosis, though often at lower levels than contemporary industrialized populations.[5] Interestingly, this suggests that the disease is not solely the result of a modern, fast-food lifestyle combined with lack of exercise. Moreover, markers of early atherosclerotic-like vascular changes have also been identified in non-human primates and other mammals, for example monkeys and pigs, suggesting that atherosclerosis may have very deep evolutionary roots.[6,7] These atherosclerotic lesions developed even when the animals were fed their natural diet. This suggests that the development of atherosclerosis is in fact inherent in primate and other mammalian biology and not only the result of following a modern lifestyle.

Considering that atherosclerosis would seem to be connected to mammalian biology and particularly human biology, why were genes associated with cardiovascular disease not selected against throughout our evolutionary past? The answer appears to be two-fold. First, atherosclerosis has negative impacts on morbidity and mortality largely only in later ages, when reproduction has ceased. Thus, there will not be selection against such genes, as they are already passed on to the next generation. Harmful disease genes that affect individuals at younger ages will gradually become less common with the passing of evolutionary time while genes that increase fertility will become progressively more common.

In a recent article in *Circulation*, Thomas, Trumble, and Thompson suggest that many genes that increase the risk for atherosclerosis late in life result in increased fertility at an earlier time when reproduction is occuring.[8] This dual nature of a gene, beneficial at one point in life but not in another phase, has been suggested before with respect to the BRCA 1/2 gene. Research in natural fertility populations suggests that BRCA1/2 carriers have higher fertility, but then excessive post-reproductive mortality.[9] Pleiotropic effects of alleles that increase reproduction have also been observed in relation to the APOE4 allele which increases the risk of later life Alzheimer's disease but is also associated with increased fertility at younger ages.[10,11]

There is evidence that genetic predisposition to atherosclerosis is associated with increase fertility making it more likely to remain common in human populations. Simply put, one gets benefits to fertility when young and detrimental morbidity and mortality when old. Byars and co-investigators and others studied the effect on fertility of genetic variants linked to atherosclerosis in a variety of human populations.[12,13] They observed that the presence of genes favoring the development of atherosclerosis was associated with increased fertility; thereby suggesting that these predisposing genes would become increasingly common in subsequent generations.

This population model appeals to me since, as noted, we have a similar situation with the genes for BRCA 1/2 and EPOE4. In an evolutionary sense, a genetic proclivity for atherosclerosis gives early benefit, ie, increased fertility at the expense of disease later in life. Since these genes increase fertility, they will become increasingly common in succeeding generations. This model thus accounts for the common occurrence of atherosclerotic disease in our current human population.

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As always, we comments are welcome at jalpert@arizona.edu.

Declaration of competing interest

None.

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References

1. Allam AH, Thompson RC, Wann LS, Miyamoto MI, El-Din Ael-H N, El-Maksoud GA, Al-Tohamy Soliman M, Badr I, El-Rahman Amer HA, Sutherland ML, Sutherland JD, Thomas GS. Atherosclerosis in ancient Egyptian mummies: the Horus study. *JACC Cardiovasc Imaging* 2011;4(4):315–27. https://doi.org/10.1016/j.jcmg.2011.02.002 PMID: 21466986.
2. Thompson RC, Allam AH, Lombardi GP, Wann LS, Sutherland ML, Sutherland JD, Soliman MA, Frohlich B, Mininberg DT, Monge JM, Vallodolid CM, Cox SL, Abd el-Maksoud G, Badr I, Miyamoto MI, el-Halim Nur el-Din A, Narula J, Finch CE, Thomas GS. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. *Lancet* 2013;381(9873):1211–22. https://doi.org/10.1016/S0140-6736(13)60598-X Epub 2013 Mar 12PMID: 23489753.
3. Murphy W.A. Jr, Nedden Dz D, Gostner P, Knapp R, Recheis W, Seidler H. The iceman: discovery and imaging. *Radiology* 2003;226(3):614–29. https://doi.org/10.1148/radiol.2263020338 Epub 2003 Jan 24PMID: 12601185.
4. Clarke EM, Thompson RC, Allam AH, Wann LS, Lombardi GP, Sutherland ML, Sutherland JD, Cox SL, Soliman MA, Abd el-Maksoud G, Badr I, Miyamoto MI, Frohlich B, Nur el-din AH, Stewart AF, Narula J, Zink AR, Finch CE, Michalik DE, Thomas GS. Is atherosclerosis fundamental to human aging? Lessons from ancient mummies. *J Cardiol* 2014;63(5):329–34. https://doi.org/10.1016/j.jjcc.2013.12.012 Epub 2014 Feb 28PMID: 24582386.
5. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Thomas GS. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* 2017;389(10080):1730–9.
6. Clarkson TB, Prichard RW, Netsky MG, Lofland HB. Atherosclerosis in pigeons; its spontaneous occurrence and resemblance to human atherosclerosis. *AMA Arch Pathol* 1959;68(2):143–7 PMID: 13669834.
7. Middleton CC, Clarkson TB, Lofland HB, Prichard RW. Atherosclerosis in the squirrel monkey. Naturally occurring lesions of the aorta and coronary arteries. *Arch Pathol* 1964;78:16–23 PMID: 14148743.
8. Thomas GS, Trumble BC, Thompson RC. Possible evolutionary origins of atherosclerosis: suggestive evidence from ancient to modern populations. *Circulation* 2025;152(19):1323–5. https://doi.org/10.1161/CIRCULATIONAHA.125.075848 Epub 2025 Nov 10PMID: 41212938.
9. Smith KR, Hanson HA, Mineau GP, Buys SS. Effects of BRCA1 and BRCA2 mutations on female fertility. *Proc R Soc B* 2012;279(1732):1389–95.
10. Trumble BC, Charifson M, Kraft T, Garcia AR, Cummings DK, Hooper P, Lea AJ, Eid Rodriguez D, Koebele SV, Buetow K, Beheim B, Minocher R, Gutierrez M, Thomas GS, Gatz M, Stieglitz J, Finch CE, Kaplan H, Gurven M. Apolipoprotein-ε4 is associated with higher fecundity in a natural fertility population. *Sci Adv* 2023;9(32):eade9797. https://doi.org/10.1126/sciadv.ade9797 Epub 2023 Aug 9PMID: 37556539PMCID: PMC10411886.
11. van Exel E, Koopman JJE, Bodegom D, Meij JJ, Knijff P, Ziem JB, Finch CE, Westendorp RGJ. Effect of APOE ε4 allele on survival and fertility in an adverse environment. *PLOS One* 2017;12:e0179497.
12. Byars SG, Huang QQ, Gray LA, Bakshi A, Ripatti S, Abraham G, Stearns SC, Inouye M. Genetic loci associated with coronary artery disease harbor evidence of selection and antagonistic pleiotropy. *PLoS Genet* 2017;13(6):e1006328. https://doi.org/10.1371/journal.pgen.1006328 PMID: 28640878PMCID: PMC5480811.
13. Byars SG, Voskarides K. Antagonistic pleiotropy in human disease. *J Mol Evol* 2020;88(1):12–25.

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