

Could androgens be relevant to partly explain why men have lower life expectancy than women?

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Life expectancy is about 5 years shorter for men than for women.¹ At any given age, men are more vulnerable than women to death from most major causes, including infections, cancer and cardiovascular disease.¹ Lifestyle and stress undoubtedly play the same role in this disparity as in other health disparities, particularly given historically higher smoking rates for men than for women. Whether these factors provide a comprehensive explanation and actionable targets of intervention is less clear, particularly as these factors do not fully explain men's cardiovascular disadvantage.² Here, to provide another perspective, the sexual disparity in life expectancy is considered in the context of an existing well-established theory from evolutionary biology. Life history theory suggests that animals, including humans, employ environmentally driven strategies to maximise Darwinian fitness, that is, reproductive success.³ Optimal strategies for reproductive success likely differ by sex, because men may have far more children than women⁴ but reproductive costs are far higher for women. As such, not only does a strategy aimed at fitness differ from the public health goal of long and healthy life but may also have sex-specific implications, and so be relevant to the shorter lifespan in men than in women.

Specifically, life history strategies may involve trading off growth or reproduction against longevity,³ with the role of less growth well known but suppressing the reproductive axis may also increase lifespan;⁵ and promoting the reproductive axis may reduce lifespan. For example, a high-protein diet in mice results in bigger gonads and shorter life, while a high-carbohydrate diet results in smaller

gonads and longer life;⁶ interestingly mice prefer a higher protein diet.⁶ In humans, the reproductive axis in women is suppressed at menopause, and artificial supplementation with reproductive hormones in postmenopausal women is not beneficial for lifespan.⁷ In contrast, men continue to be fertile throughout adult life; little consideration has been given to whether lifelong fertility in men relates to or trades off against lifespan. Given the shorter lifespan for men than for women, consideration is given here to how male reproductive hormones, namely, androgens, affect health in men beyond reproduction, and whether androgens could have any relevance to the sexual disparity in life expectancy, or any implications for the prevention and treatment of the leading causes of mortality.

NON-REPRODUCTIVE EFFECTS OF ANDROGENS IN MEN

Currently, the non-reproductive effects of androgens on men's health is little researched.⁸ The published literature also suffers from citation bias towards studies putting testosterone in a positive light.⁹

Observational evidence concerning endogenous testosterone is difficult to interpret because the most commonly measured androgen biomarker, serum testosterone, falls in men with obesity and ill-health.¹⁰ Observed inverse associations of serum testosterone with major causes of mortality, such as cardiovascular disease, may be confounded in men by health status and so be difficult to interpret, as the authors of the relevant systematic reviews and meta-analyses have been careful to note.^{11–13} Other androgen biomarkers that give observational associations more similar to results from randomised controlled trials (RCTs) for ischaemic heart disease or its risk factors are rarely reported.¹⁴ Similarly, observationally, androgens do not predict prostate cancer,¹⁵ but genetic studies have removed doubts about a role for androgens in prostate cancer.¹⁶ Observational evidence concerning exogenous testosterone prescription in men is mixed,^{17–20} and difficult to interpret because of the possibility of bias by indication and/or

immortal time,²¹ which may generate findings at variance with meta-analysis of RCTs.^{20 22–24} The only observational study of testosterone prescription that used a self-comparison and a control exposure is probably the most convincing: it found, specifically, that testosterone prescription was associated with a higher risk of non-fatal myocardial infarction.²⁵

Evidence about the effects of androgens from RCTs is limited because the US Institute of Medicine advised, in 2004, that no large scale trials of testosterone should be undertaken until benefits over existing treatments had been established in small trials.²⁶ Health comparisons between men with genetically higher or lower androgens using Mendelian randomisation are limited because androgens are rarely measured, so few genetic variants reliably determining androgens have been identified.^{27 28}

Nevertheless, information about the role of androgens in men's health is slowly emerging. Below, the effects of androgens on major contributors to global mortality are considered, including immune function, cancer, cardiovascular disease and diabetes. Given the focus on the effects of androgens, greatest emphasis is placed on evidence about likely causal effects from RCTs, Mendelian randomisation, experiments, natural experiments and knockout animal models, rather than observed associations.

Immune function

Androgens are generally understood to suppress the immune system;^{29–32} whereas oestrogen promotes immune response.³³ For example, testosterone may inhibit CD4 T-cell function,³⁰ while androgen deprivation is associated with enlargement of the thymus, which promotes immune function.²⁹ Experiments in rodents suggest androgens are pro-inflammatory and delay wound healing.^{34 35}

Men tend to be more vulnerable to infections than women.^{33 36 37} Lifestyle undoubtedly plays a part. However, the male vulnerability is most evident at ages when sexual dimorphism in sex hormones is greatest, those being, early infancy, puberty and young adult life, and includes periods, such as early infancy, when lifestyle choices are unlikely to differ by sex.³⁷ Male disadvantage is less evident for infections where a pathological immune response occurs.³⁷

On the other hand, androgens may have the benefit of suppressing autoimmune responses,^{29–31} consistent with men being less vulnerable to autoimmune diseases than women,^{29 31} with the difference

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emerging at puberty. Androgen administration has shown some promise in trials as a treatment for rheumatoid arthritis.^{38–39} Whether biological treatments for autoimmune diseases, such as tumour necrosis factor- α inhibitors, operate via a similar mechanism, is unknown.

Cancer

Given androgens' suppressive effects on immune function,^{29–32} androgens are thought to play a role not only in prostate and testis cancer, but also in cancer more generally,²⁹ although evidence in men is scarce. Based on androgen knockout models, androgens could play a permissive role in several cancers with a male preponderance,⁴⁰ including cancer of the bladder,⁴¹ kidney,⁴² liver,⁴³ and lung,⁴⁴ as well as, perhaps, of the esophagus⁴⁵ and colorectum.⁴⁶ Castration protects male rats against colonic adenomas.⁴⁶ Whether androgens contribute to men's vulnerability to cancer, and whether cancers with male predominance share features, has not been comprehensively investigated. Androgens' role in immune function also raises questions about other major chronic diseases with an inflammatory component^{47–48} to which men are more vulnerable, such as cardiovascular disease.

Cardiovascular disease

Men have higher cardiovascular disease mortality rates than women,⁴⁹ particularly at the period in life, early adulthood, when male hormones are highest.^{49–50} However, haemorrhagic stroke mortality rates differ little by sex,⁵¹ suggesting that the relevant causative factor underlying men's cardiovascular disadvantage is specific to processes that drive non-haemorrhagic forms of cardiovascular disease, such as ischaemia, thrombosis, embolism and aneurysm. Notably, androgens may raise clotting factors, such as thromboxane.^{52–53}

Currently, at the same level of the major risk factors for atherosclerotic cardiovascular disease, specifically, age, smoking, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, blood pressure and diabetes, validated risk prediction models give substantially higher absolute risk for men than for women.⁵⁴ Although menopause precedes an increase in ischaemic heart disease rates for women,⁵⁵ RCTs have shown that oestrogen does not protect against cardiovascular disease in either men⁵⁶ or women.⁷ Recent promotion of highly profitable testosterone to older men as an antidote to ageing has led to warnings about the cardiovascular risk of testosterone from regulators. In June

2014, the US Food and Drug Administration (FDA) added a warning about venous blood clots to the testosterone product label.⁵⁷ In July 2014, Health Canada warned about "serious and possible life-threatening heart and blood vessel problems such as heart attack, stroke, blood clot in the lungs or legs; and increased or irregular heart rate with the use of testosterone replacement products".⁵⁸ The European Medicines Agency was less clear in November 2014,⁵⁹ but advised that testosterone should be restricted to men with pathological hypogonadism.⁵⁹ In March 2015, the US FDA warned about "the possible increased risk of heart attacks and strokes associated with testosterone use" and required a label change.⁶⁰ Sales of testosterone are already falling in the USA⁶¹ and litigation against pharmaceutical companies is underway.⁶²

These warnings from regulators about the cardiovascular risk of testosterone^{57–60} suggest that substantially higher androgens in men than women could underlie higher cardiovascular disease mortality rates in men than in women, although any adverse effects of exogenous androgens in unhealthy older men^{57–60} might not translate to endogenous androgens in healthy men. In addition, few androgen-related genetic variants have been found in genome-wide association studies of cardiovascular disease. However, few such studies are sex-specific, few androgen related genetic variants have been identified^{27–28} and many genetic variants are of unknown function, so this may be absence of evidence rather than evidence of absence.

The known effects of testosterone administration in men from meta-analyses of RCTs, include lower HDL-cholesterol,⁶³ higher haemoglobin,⁶³ lower adiponectin⁶⁴ and higher risk of venous thrombosis.²² Some of these changes also take place in boys at puberty under the influence of endogenous testosterone,⁶⁵ suggesting similar effects of exogenous and endogenous testosterone. Mendelian randomisation studies also suggest endogenous testosterone lowers HDL-cholesterol⁶⁶ as well as possibly raising heart rate,⁶⁷ consistent with the warning from Health Canada, and again suggesting similar effects of endogenous and exogenous testosterone. Most systematic reviews and meta-analyses of RCTs have shown non-significantly higher risk of cardiovascular events on testosterone,^{68–71} but are underpowered, partly because of incomplete event reporting in the underlying RCTs,⁷⁰ and, in one meta-analysis, a

numerical error (reporting on 308 instead of 485 men).⁶⁹ Notably, the most recent trial of testosterone found 12 major adverse cardiovascular events among 155 men in the treatment arm and 4 among 151 men in the placebo arm, OR 3.08, 95% CI 0.97 to 9.79.⁷² Men with lower endogenous testosterone due to legal castration have relatively lower rates of specifically myocardial infarction.⁷³ Similarly, men with lifelong low testosterone due to Klinefelter's syndrome have low rates of ischaemic heart disease,⁷⁴ despite well-known vulnerability to diabetes.⁷⁵

Diabetes

Diabetes is a strong, well-established risk factor for cardiovascular disease, although sex differences in diabetes rates are minor and inconsistent.⁷⁶ RCTs suggest androgens improve glucose metabolism,⁷⁷ perhaps through building muscle mass, which is a sink for glucose disposal. Whether treatments for diabetes operate by raising androgens has rarely been assessed. However, insulin may raise androgens,⁷⁸ which could be relevant to the difference in magnitude between observed and causal estimates for the association of diabetes with cardiovascular disease.⁷⁹

ENVIRONMENTAL DRIVERS OF ANDROGENS

Despite the potential benefits of androgens for some autoimmune diseases and diabetes, consideration of the possibility that androgens could have a role in chronic diseases with a male preponderance would be consistent with evolutionary biology and the newly emerging evidence, as well as potentially providing aetiological insight concerning some diseases acknowledged to be poorly understood.² Many may feel that such a perspective would not be useful in clinical or public health practice because antiandrogens would be unacceptable to men. However, understanding alone could be valuable. For example, androgens lowering HDL-cholesterol and raising cardiovascular disease risk could underlie the observed inverse association of HDL-cholesterol with cardiovascular disease and thereby explain the failure of HDL-cholesterol raising therapies in cardiovascular disease.⁸⁰ Similarly, androgens generating systemic inflammation and raising cardiovascular risk could explain the failure of several anti-inflammatories.⁸¹ Pharmaceutical companies are investing less in cardiovascular therapies⁸² following expensive failures with lipid modulators and anti-inflammatories, highlighting the need for

new approaches. Moreover, antiandrogens are quite widespread and in therapeutic use. Obesity in men reduces testosterone.⁸³ Antiandrogens are used in prostate cancer. Several therapies for cardiovascular disease have anti-androgen properties, such as spironolactone, statins⁸⁴ and perhaps digoxin.⁸⁵ Whether any other therapies for cardiovascular disease currently in use or being trialled, such as diuretics or methotrexate,⁸¹ reduce androgens is unknown. Diuretics are thought to affect sexual function adversely.

Whether androgenic effects could potentially provide a new classifying principle for common modifiable environmental exposures as healthy or otherwise has rarely been considered. Environmental drivers of androgens are usually conceptualised as xenobiotic endocrine disruptors disrupting androgens, with harmful effects.⁸⁶ However, evolutionary biology would predict that androgens in men should be sensitive to environmental indicators of breeding conditions, so as to focus reproductive effort at suitable times while minimising the risk attached to extreme masculinity, which may have been selected against in human history.⁸⁷ Few common modifiable exposures are known to affect testosterone, apart from obesity in men, driven by the conversion of testosterone to oestrogen in fat cells.⁸³ As might be expected, chronic undernutrition reduces testosterone.⁸⁸ However, the physiological processes that regulate testosterone in response to environmental conditions have not been systematically investigated. Androgens are sensitive to environmental influences, because they share metabolism and catabolism pathways with major drugs, foods and environmental exposures.⁸⁹ These catabolism pathways have been studied in the context of drug–drug interactions,⁹⁰ are polymorphic,⁸⁹ and are susceptible to epigenetic programming during early life.⁹¹ Notably, diclofenac,⁹² rofecoxib,⁹³ ibuprofen⁹² and nicotine,⁹⁴ all inhibit these pathways, thereby most likely raising androgens, and all have unexpected adverse cardiovascular side effects.^{95 96} Testing common modifiable exposures, selected according to their role in androgen metabolism or catabolism, for their effects on androgens in vitro, might provide a preliminary classification of exposures as potentially adverse or protective for further investigation in vivo.

CONCLUSION

Considering androgens as potential contributors to major diseases represents a major paradigm shift that flies in the face

of individual level data from observational studies. However, in addition to experimental evidence and warnings from regulators, relevant physiological pathways exist. Androgens suppressing the immune system could increase vulnerability to infections and cancer. Androgens increasing clotting could increase vulnerability to cardiovascular disease. Despite some benefits of androgens for autoimmune diseases and diabetes, men have shorter lives than women. Current understanding of major chronic diseases is incomplete. Surely, we should capitalise on the insight unexpectedly provided by commercial promotion of androgens to older men to rethink the role of androgens, particularly, in immune function, cancer and cardiovascular disease, as potentially providing an underlying explanatory mechanism that could address the major sexual disparity in life expectancy, help identify new specific targets of intervention, explain unexpected side effects of commonly used drugs and eventually provide targets for precision medicine.

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