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Article

Reproduction and longevity: A Mendelian randomization study of gonadotropin-releasing hormone and ischemic heart disease

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ABSTRACT

Background: According to well-established evolutionary biology theory there is a trade-off between reproduction and longevity, implying that upregulating the reproductive axis might drive major diseases. We assessed whether the central driver of reproduction gonadotropin-releasing hormone 1 (GnRH1) had a causal effect on the leading cause of global morbidity and mortality, i.e. ischemic heart disease (IHD). As a contrast we similarly examined the role of GnRH2 because it is more a driver of female sexual behavior.

Methods: We applied strong (p-value $< 5 \times 10^{-6}$) and independent genetic predictors of GnRH1 and GnRH2 to an extensively genotyped IHD case (n = 76,014) - control (n = 264,785) study and combined the genetic variant specific Wald estimates using inverse variance weighting (IVW) with multiplicative random effects, and as a sensitivity analysis used weighted median, MR-Egger and MR-PRESSO estimates, and repeated the analysis only using genome wide significant genetic predictors.

Findings: GnRH1, predicted by 11 genetic variants, was positively associated with IHD (IVW odds ratio (OR) 1.04 per effect size, 95% confidence interval (CI) 1.01 to 1.08), but GnRH2, predicted by 15 genetic variants, was not (IVW OR 0.98, 95% CI 0.95 to 1.02). Estimates from sensitivity analysis were similar.

Interpretation: GnRH1 is a potential IHD genetic target. Apart from demonstrating a central tenet of evolutionary biology in humans, our study suggests that existing treatments and environmental factors targeting GnRH1, its drivers or consequences could be re-purposed to prevent and treat IHD. Given, the importance of reproduction to the human species, many such exposures likely exist.

Background

Economic development has led to lifespan approximately doubling from pre-industrial norms (Canudas-Romo, 2010), and the emergence of non-communicable diseases, particularly cardiovascular disease (CVD), as leading causes of global morbidity and mortality (GBD 2017 Causes of Death Collaborators, 2018; GBD 2017 DALYs and HALE Collaborators, 2018). CVD reduction is vital to achieving the Sustainable Development Goals (Nugent et al., 2018). Declines in CVD in recent decades in Western Europe and North America are attributed to effective treatments and changes in pleiotropic adult risk factors aimed at preserving health generally, particularly the reduction in tobacco use (O'Flaherty, Buchan, & Capewell, 2013). However, variations in CVD by geography, level of economic development, ethnicity, socio-economic position and sex (Howrey, Goodwin, Eschbach, & Freeman, 2010; González, Rodríguez Artalejo, & Calero, 1998; Nikiforov & Mamaev, 1998) are difficult to explain comprehensively in terms of existing treatments and established adult risk factors (Ezzati et al., 2015; Havranek et al., 2015). Moreover, several treatments targeting well-established CVD risk factors, such as lipids, have failed in late-stage randomized controlled trials (RCTs) (Armitage, Holmes, & Preiss, 2019; Canner et al., 1986; Landray et al., 2014). Meanwhile, new, unexpected, unexplained and, likely causal, common risk factors for CVD have recently emerged, such as clonal hematopoiesis (Jaiswal et al., 2017) and reticulocytes (Astle et al., 2016), while questions have arisen as to whether existing CVD treatments are acting on genetically valid targets (Schooling et al., 2018). Taken together these developments have highlighted the importance of comprehensive explanatory models of population health as a means of identifying effective ways to prevent, treat and ultimately eliminate CVD equitably.

Abbreviations: CVD, cardiovascular disease; GWAS, genome-wide association study; GnRH, Gonadotropin-releasing hormone; IHD, ischemic heart disease; SNP, single nucleotide polymorphism

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Study of CVD currently includes a wide range of perspectives addressing the key question of how the embodiment of social and environmental factors occurs, with particular interest in the role of early life factors and "stress" (Havranek et al., 2015). The developmental origins of health and disease, inspired by observations from Europe of ischemic heart disease (IHD) associated with very limited early life conditions (Barker & Osmond, 1986; Forsdahl, 1977), has been very influential in re-conceptualizing health from a life course perspective, with an emphasis on the role of adaption to early life conditions affecting health throughout life (Bateson et al., 2004). The World Health Organization considers low birth weight, a key indicator of an early adverse environment, as a risk factor for CVD (WHO). Nevertheless, effects of birth weight on IHD remain controversial because socioeconomic position or genetics could drive observed inverse associations of birth weight with IHD (Horikoshi et al., 2016), particularly given that this association is not evident in monozygotic twins (Oberg, Cnattingius, Sandin, Lichtenstein, & Iliadou, 2011). However, more complex conceptualizations of the role of early growth taking into account maternal factors (Wells, 2019), may yet yield insight. Childhood infections as a driver of lifelong inflammation and thereby non-communicable diseases (Finch & Crimmins, 2004) has been very influential in high-lighting the role of inflammation in health, and can be thought of more broadly as one of the many stressors that contributes to allostatic load (McEwen, 1998) and thereby CVD (Havranek et al., 2015). RCTs of anti-inflammatories in CVD have not yet yielded any new treatments (Libby & Everett, 2019), but not all anti-inflammatory pathways have been exhaustively examined (Libby et al., 2018). The lowest level of IHD ever recorded was found in a forager-horticulturalist population heavily exposed to infection (Kaplan et al., 2017). These empirically derived theories of population health still have the potential to deliver important new insights and interventions, but do not provide comprehensive explanatory models, to guide the selection of new targets of intervention. To provide a more theoretical basis population health, chronic disease and particularly CVD has been increasingly reconceptualized in different ways using well-established evolutionary biology theory (Schooling et al., 2011; Stearns, 2005; Wells, 2000), complimentary to the application of evolutionary biology for the prevention and control of infectious diseases (Alizon & Methot, 2018; Reiber & Moore, 2010).

Evolutionary biology highlights that all organisms, including humans, have been shaped to maximize reproductive success rather than lifespan, so promoting reproductive success (fitness) may take precedence over lifespan on both a psychological and a physiological level. This key insight can be used to place the developmental origins of health and disease within a theoretical context where life history theory (Stearns, 1976) can be used to predict how different environments might affect key traits including birth size, growth rates, age at maturity, number of children and lifespan (Wells, Nesse, Sear, Johnstone, & Stearns, 2017). In addition, the idea that there is a trade-off between growth and reproduction one the one hand and longevity on the other hand provides some explanation for the changes in patterns of disease with the epidemiological transition (Schooling & Leung, 2010). Drivers of growth trading of against longevity underpins the investigation of dietary restriction mimetics in CVD (Winnik, Auwerx, Sinclair, & Matter, 2015). Drivers of reproduction trading of against longevity has been used recently to identify potential interventions for CVD, such as protein C (Schooling & Zhong, 2017), neurokinin 3 receptor antagonists (Schooling, 2017), copper and zinc (Kodali, Pavilonis, & Schooling, 2018) and aspartate (Zhao, Kwok, & Schooling, 2019). Genetic selection in favour of both fertility and IHD has been demonstrated (Byars et al., 2017). Physiologically reproduction is driven centrally by gonadotropin-releasing hormone 1 (GnRH1) (Desaulniers, Cederberg, Lents, & White, 2017). To ensure optimal timing of reproduction GnRH is likely regulated by many modifiable, environmental factors, which could provide new targets for IHD prevention or treatment. Some drivers of GnRH are already known to be related to IHD, specifically insulin which increases GnRH (Sliwowska et al., 2014) also increases IHD (Tikkanen et al., 2016; Zhan et al., 2017), while nitric oxide which decreases GnRH (Bellefontaine et al., 2011) is a component of one of the oldest treatments for IHD, i.e., nitroglycerin.

To our knowledge, no previous studies have examined the association of exogenous or endogenous GnRH with IHD. GnRH agonists and antagonists are used to modulate hormones, particularly in relevant cancers (Clinton, Woldu, & Raj, 2017). Observationally, GnRH agonists increase the risk of CVD in prostate cancer patients (Bosco et al., 2015); these studies of treatments are open to bias by indication. Few RCTs in prostate cancer patients have been conducted to assess or compare the effects of GnRH agonists and antagonists on CVD (Nguyen et al., 2011; Sciarra et al., 2016), although a comparative trial (NCT02663908) is now underway. As such, the RCT evidence does not provide a clear guide to the role of GnRH in general or in IHD. To address this gap, we used two-sample Mendelian randomization to estimate the causal effect of specifically GnRH1 on IHD in the general population using genetic predictors of GnRH1 from a proteomics genome wide association study (GWAS) applied to the largest publicly available genetic study of IHD, enabling us to obtain an estimate even though no study measuring both GnRH1 and IHD events exists. Genetic make-up is determined randomly at conception, so comparing IHD events by genetically predicted levels of GnRH1, gives randomization akin to that in a randomized controlled trial (Smith & Ebrahim, 2003), and thereby unconfounded estimates, in contrast to associations of exposure with outcome that are open to confounding by possible common causes of exposure and outcome, such as socio-economic position, life style and health status. We also considered GnRH2, because it is more a driver of female sexual behavior than of reproduction (Desaulniers et al., 2017; Okubo & Nagahama, 2008; Urbanski, 2012), so GnRH1 would be expected to have more of an effect on IHD than GnRH2.

Materials and methods

Gonadotropin-releasing hormone 1 and 2

Genetic associations with GnRH1 and GnRH2 protein were obtained from a GWAS (n = 3301; mean age, 43.7 years; 1615 women [49%]) of people of European descent (Sun et al., 2018) providing publicly available genetic summary statistics. Genetic associations with rank inverse normalized residuals were obtained from linear regression of natural log-transformed protein abundances adjusted for age and sex, duration between blood draw and processing and the first three principal components of ancestry from multidimensional scaling to account for population stratification (Sun et al., 2018).

We used all single nucleotide polymorphisms (SNPs) which independently ($r^2 < 0.05$) and strongly (p-value $< 5 \times 10^{-6}$) predicted GnRH1 or GnRH2. We used the "clump_data" function of MRBase (Hemani et al., 2018) to select between correlated SNPs (i.e., in linkage disequilibrium). We used highly correlated proxy SNPs for all genetic variants with ambiguous allele coding to ensure that SNPs were aligned on the same allele for both exposure and outcome. Palindromic SNPs with allele coding A/T or C/G cannot be unequivocally aligned without additional information. We assessed the strength of genetic instruments from the F-statistic using an approximation (Bowden et al., 2016b), where an F-statistic > 10 makes weak instrument bias less likely. To assess if the SNPs were "randomized" as expected we checked they were not associated with key potential confounders of the association of GnRH1 or GnRH2 with IHD, including current smoking, age at completion of full-time education, Townsend index, alcohol intake frequency and number of days per week walked for 10 + minutes, at Bonferroni corrected significance in the UK Biobank GWAS summary statistics (https://github.com/Nealelab/UK_Biobank_GWAS) of ≤361,194 people of white British ancestry. To assess whether the SNPs might affect IHD other than via GnRH we searched two curated genotype to phenotype cross-references, Ensembl release 94 (http://useast.

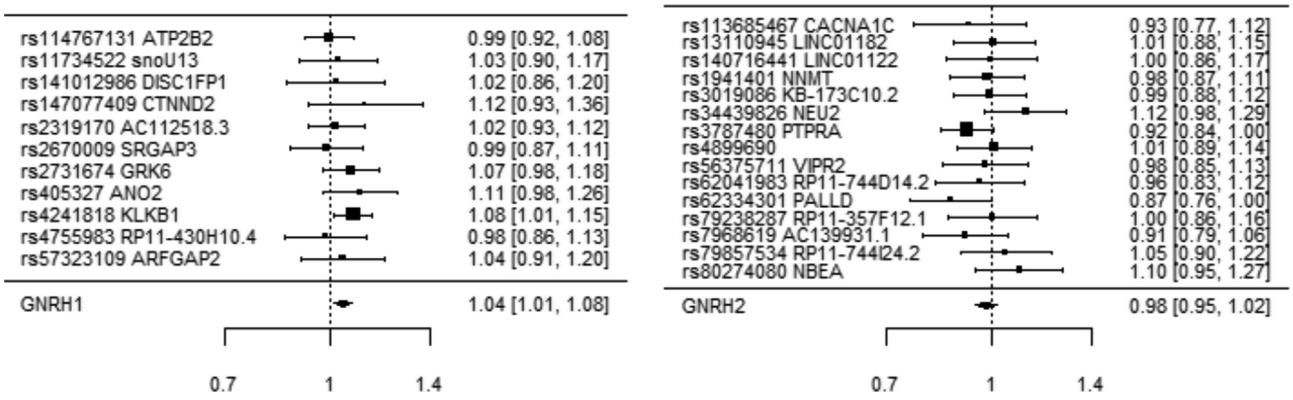

Fig. 1. Overall IVW (random effects) and SNP-specific estimates for the association of (a) GnRH1 and (b) GnRH2 with IHD.

ensembl.org/index.html) and PhenoScanner (Staley et al., 2016), which gives known associations of SNPs with diseases and health-related traits. We searched for paths by which the SNPs predicting GnRH1 or GnRH2 might affect IHD other than via GnRH1/2. We searched PhenoScanner for diseases and traits associated with the SNPs (or their correlates $r^2 > 0.8$) at p-value $< 1 \times 10^{-5}$.

Ischemic heart disease

Genetic associations with IHD were obtained from the largest publicly available extensively genotyped IHD study (cases = up to 76,014, non-cases = up to 264,785) based on a meta-analysis of the CARDIoGRAPMplusC4D 1000 Genomes case (n = 60,801)-control (n = 123,504) study/MIGen/CARDIoGRAM Exome chip study, the interim release UK Biobank SOFT CAD study (cases = 10,801, controls = 137,371), and two case (n = 4120)-control (n = 3910) studies from Germany and Greece (Nelson et al., 2017). CARDIoGRAMplusC4D 1000 Genomes participants are largely of European descent (77%) with detailed phenotyping based on medical records, clinical diagnosis, procedures that indicate IHD, such as revascularization, and/or angiographic evidence of stenosis, and sometimes case status ascertained from medications or symptoms that indicate angina or from self-report (Nikpay et al., 2015). In the UK Biobank SOFT CAD GWAS (94% European ancestry) the case phenotype included fatal or nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, chronic IHD and angina. Controls were defined as individuals WHO were not a case after exclusions (Nelson et al., 2017). To check for differences between data sources we also obtained separate estimates for CARDIoGRAPMplusC4D 1000 Genomes and the entire UK Biobank. For the UK Biobank, we used publicly available genetic summary statistics for IHD, obtained from 408,458 white British UK Biobank participants, with 31,355 cases defined based on PheWAS code 411 (Zhou et al., 2018). Estimates were adjusted for sex, birth year and the first 4 principal components of ancestry (Zhou et al., 2018). A generalized mixed model with saddlepoint approximation was used to obtain precise estimates despite even the imbalance of cases to controls (Zhou et al., 2018).

Statistical analysis

SNP-specific Wald estimates were meta-analyzed using inverse variance weighting (IVW) with multiplicative random effects. SNP-specific Wald estimates were calculated as the quotient of the estimate for SNP on IHD and the estimate for SNP on GnRH1 or GnRH2. As sensitivity analysis we used a weighted median, which may provide correct estimates if the SNPs are invalid instruments for < 50% of the weight (Bowden, Davey Smith, Haycock, & Burgess, 2016a), MR-Egger, which is robust to pleiotropy assuming the instrument strength is independent of the direct effect (Burgess & Thompson, 2017), and Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO), which detects potentially pleiotropic SNPs from the residual sum of squares and removes statistically significant outliers (Verbanck, Chen, Neale, & Do, 2018). As an additional sensitivity analysis, we repeated the analysis using SNPs predicting GnRH1 or GnRH2 at p-value $< 5 \times 10^{-8}$. We used the R packages "MendelianRandomization" and "MRPRESSO" to obtain estimates. We used R (version 3.5.1, The R Foundation for Statistical Computing, Vienna, Austria) for our analysis.

Ethics

We used publicly available summary data with no direct involvement of participants in the study. No ethical approval is required.

Results

Of the 225 SNPs predicting GnRH1 at 5×10^{-6} one of the 12 independent SNPs (rs145898851) was not available for IHD and had no proxy with $r^2 > = 0.5$, giving 11 SNPs, of which the two palindromic SNPs were replaced by proxies (rs28529564 by rs114767131 ($r^2 = 0.59$) and rs11039086 by rs57323109 ($r^2 = 0.95$)). Of the 123 SNPs predicting GnRH2 one invalid SNP (chromosome position, 20:2975929) was discarded. Of the 15 independent SNPs, rs34246308 was not available for IHD and was replaced by rs1941401 ($r^2 = 0.98$) and two palindromic SNPs were replaced by proxies (rs79590491 by rs79238287 ($r^2 = 0.84$), and rs6999411 by rs3019086 (r2 = 0.50)). The F-statistic for GnRH1 was 33 and for GnRH2 was 24. None of the SNPs were associated with key potential confounders of GnRH1 or GnRH2 on IHD in the UK Biobank.

GnRH1 was positively associated with IHD using IVW with little evidence of pleiotropy (Fig. 1a). The weighted median, MR-Egger and MR-PRESSO gave similar estimates (Table 1), again with little evidence of pleiotropy. Some genetic predictors of GnRH1 were associated with potential consequences of GnRH1 and causes of IHD (rs141012986 with height and atrial fibrillation, rs2731674 with height, coagulation factors, metabolites, interleukins, lung function, body composition, and rs4241818 with thrombosis and metabolites). GnRH2 was not associated with IHD using IVW with little evidence of pleiotropy (Fig. 1b). The weighted median, MR-Egger and MR-PRESSO gave similar estimates with little evidence of pleiotropy (Table 1). Rs34439826 predicting GnRH2 was associated with height and forced vital capacity, while rs79238287 was associated with estrogen treatment. Estimates were very similar for CARDIoGRAPMplusC4D 1000 Genomes and the entire UK Biobank considered separately (Supplementary Table 1).

At genome-wide significance, 2 SNPs (rs4241818 and rs2731674) independently predicted GnRH1 and 1 SNP (rs3787480) predicted GnRH2. Based on these two SNPs GnRH1 was positively associated with IHD (IVW with fixed effects odds ratio, 1.08; 95% confidence interval, 1.02 to 1.14). Based on rs3787480 GnRH2 was not associated with IHD

Table 1
Mendelian randomization estimates for associations of GnRH1 (based on 11 independent SNPs with p-value $< 5 \times 10^{-6}$) and GnRH2 (based on 15 independent SNPs with p-value $< 5 \times 10^{-6}$) with IHD, using a study largely based on CARDIoGRAPMplusC4D 1000 Genomes and the UK Biobank SOFT CAD.

Exposure	Mendelian randomization method	Odds ratio	95% confidence interval	p-value	Cochran's Q statistic (p-value)	MR-Egger	
						Intercept p-value	I^2
GnRH1 effect size	Inverse variance weighted	1.04	1.01, 1.08	0.01	6.06 (0.81)	–	–
	Weighted median	1.04	1.00, 1.09	0.08	–	–	–
	MR-Egger	1.02	0.93, 1.13	0.61	5.92 (0.75)	0.70	75.5%
	MR-PRESSO (corrected)	1.04	1.03, 1.05	0.01		–	–
GnRH2 effect size	Inverse variance weighted	0.98	0.95, 1.02	0.29	13.3 (0.50)	–	–
	Weighted median	0.99	0.94, 1.04	0.64	–	–	–
	MR-Egger	0.98	0.88, 1.10	0.75	13.3 (0.43)	0.99	0.0%
	MR-PRESSO (corrected)	0.98	0.95, 1.02	0.30		–	–

(Fig. 1b).

Discussion

Consistent with theoretical predictions from evolutionary biology and some empirical evidence (Byars et al., 2017), this study showed GnRH1, but not GnRH2, positively associated with IHD.

This first study assessing the role of GnRH in IHD makes cost-effective use of publicly available GWAS, nevertheless several considerations bear mention. First, although the F-statistics were > 10, weak instrument bias is possible, which likely biases towards the null, but interpretation was similar in the sensitivity analysis using SNPs associated with GnRH1 or GnRH2 at genome wide significance. Second, confounding by population stratification is possible; however both samples mainly concern people of European descent from GWAS using genomic control (Nelson et al., 2017; Sun et al., 2018), and the SNPs were not associated with potential confounders, making such confounding unlikely. Third, some SNPs predicting GnRH1 were associated with factors potentially relevant to CVD, and it is unknown whether these are drivers or consequences of GnRH1. However GnRH1 is the central master of reproduction (Desaulniers et al., 2017; Okubo & Nagahama, 2008; Urbanski, 2012) suggesting vertical rather than horizontal pleiotropy, i.e., these factors are consequences of GnRH1 rather than alternative pathways that confound the association of GnRH1 with IHD. Fourth, two-sample Mendelian Randomization gives unconfounded estimates, but is open to the selection bias that may occur in observational studies (Hernan, Alonso, & Logroscino, 2008) particularly when considering a disease condition rather than mortality. Specifically, exposures have to be considered comprehensively from inception (Hernan, Sauer, Hernandez-Diaz, Platt, & Shrier, 2016) so studies of specific diseases will be biased by missing prior deaths due to the exposure from the same underlying birth cohort. However, IHD occurs at relatively young ages and death from IHD generally precedes other types of CVD (Kesteloot & Decramer, 2008), making it less open to such bias. In contrast, studies of stroke would be more open to bias but were not considered here, because IHD is a more important driver of lifespan. Fifth, GnRH1 and GnRH2 were not measured in the sample with the outcome, however genetic predictors of proteins should not vary by sample. Sixth, effects of genetic variants on IHD could vary by age or sex, but sufficiently large unbiased sex-specific samples are not available to test this possibility. However, GnRH is not known to have different physiologic effects by age in adults. Seventh, we assumed linear associations; a dose-response is taken as an indicator of a causal effect (Hill, 1965). Eighth, canalization could generate a bias, however the reproductive axis is most active before birth, during the mini-puberty of infancy and from puberty. Effects of canalization on GnRH are a known unknown. Ninth, this study largely concerns people of European descent, so it might not be generalizable to other populations. However, causes are normally consistent but not always relevant in all settings. Replication in a non-Western population is currently not possible, but would be very valuable. Tenth, reproduction affects other drivers of longevity, such as immunity (Segner, Verburg-van Kemenade, & Chadzinska, 2017), and so might be expected to promote infections and protect against auto-immune conditions. However, these predictions are difficult to test, because currently sufficiently large densely genotyped GWAS of relevant events are not available. Instead, we have been focusing on using this insight to identify potential interventions for IHD to prioritize for investigation from likely drivers of GnRH1.

Here we have sought empirical evidence that a key tenet of evolutionary biology, the trade-off between reproduction and longevity, is relevant to humans through a modifiable physiological mechanism so as inform key issues in population health and provide a means of identifying additional effective social, environmental and medical targets of intervention. For example, the optimum trade-off differing by sex, because of sex-specific life history strategies, could be relevant to the long-standing social inequality of shorter lives in men than women (Zarulli et al., 2018). In particular, whether sex-specific effects of GnRH1 on sex hormones might be relevant to higher rates of IHD in men than women not explained by current risk factors (Ezzati et al., 2015) could be considered. Prima facie interventions designed to promote fitness (as genetic contribution to succeeding generations) with health as a by-product might be expected to be more motivating than interventions directly promoting health. Appearance based smoking cessation interventions have shown some promise (Burford, Jiwa, Carter, Parsons, & Hendrie, 2013; Grogan et al., 2011). Whether stress affects GnRH1 and thereby IHD is not entirely clear, but stress has neuroendocrine effects (McEwen, 1998). From a physiological perspective this study suggests that drivers of GnRH1 might be targets of intervention for IHD. Apart from insulin and nitric oxide, potential drivers of GnRH1 include neurokinins (Skorupskaite et al., 2017, 2018), aspartate/glutamate (Dhandapani & Brann, 2000; Downing, Joss, & Scaramuzzi, 1996), gamma-aminobutyric acid (Camille Melon & Maguire, 2016) and dynorphin (Moore, Coolen, Porter, Goodman, & Lehman, 2018). Notably, a common feature of several successful treatments for IHD is suppression of the male reproductive axis, including spironolactone, a known anti-androgen, statins (Schooling, Au Yeung, Freeman, & Cowling, 2013), digoxin (Stoffer, Hynes, Jiang, & Ryan, 1973), nitric oxide (Rosselli, Keller, & Dubey, 1998) and some hypertensives (Fogari et al., 2002; Suzuki, Tominaga, Kumagai, & Saruta, 1988).

Conclusion

This study provides some empirical evidence in humans of a key aspect of evolutionary biology, i.e., the trade-off between reproduction and longevity, by showing that GnRH1, specifically, is positively associated with IHD. This study implies that GnRH1, its drivers and its consequences, are potential targets of intervention for the leading cause of global morbidity and mortality.

Declarations

Ethical approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. As such informed consent is not applicable for this study.

Availability of data and materials

This study is an analysis of publicly available data. The programs used are available on request.

Competing interests

None of the authors have any conflicts of interest.

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Author contributions

CMS had the idea. JCMN and CMS conducted the analysis independently and cross-checked. CMS drafted the manuscript. JCMN reviewed the manuscript for intellectual content and approved the final version.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2019.100411.

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