Fatherhood and the risk of cardiovascular mortality in the NIH-AARP Diet and Health Study

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Submitted on July 5, 2011; resubmitted on August 8, 2011; accepted on August 15, 2011

BACKGROUND: Fertility potential and reproductive fitness may reflect a man’s future health, given that over one-third of the male human genome is involved in reproduction. We sought to determine if offspring number predicts cardiovascular death in the US men.

METHODS: Using data from the NIH-AARP Diet and Health Study, 137,903 men (aged 50–71) without prior cardiovascular disease were followed-up for an average of 10.2 years. International Classification of Diseases, ninth edition, codes were used to establish the cause of death, and multivariable Cox proportional hazards modeling was used to estimate the association between offspring number and cardiovascular death while accounting for sociodemographic and lifestyle characteristics.

RESULTS: Almost all (92%) participants had fathered at least one child and 50% had three or more offspring. A total of 3,082 men died of cardiovascular causes during follow-up for an age-adjusted incidence rate of 2.70 per 1000 person-years. Compared with fathers, after adjusting for sociodemographic and lifestyle factors, childless men had a 17% [hazard ratio (HR): 1.17; 95% confidence interval (CI): 1.03–1.32] increased risk of death from cardiovascular disease contracted in the study period, and this elevated risk appeared to extend also to men with only one child. In comparison with fathers of five or more children, adjusted relative hazards for cardiovascular mortality of this sort were 1.06 (95% CI: 0.92–1.22) for four children, 1.02 (0.90–1.16) for three children, 1.02 (0.90–1.16) for two children, 1.11 (0.95–1.30) for one child and 1.21 (1.03–1.41) for no children.

CONCLUSIONS: Married men who have no children have a higher risk of dying from cardiovascular disease contracted after the age of 50 than men with two or more children.

Key words: infertility / male infertility / epidemiology

Introduction

Aberrations in reproductive fitness may be a harbinger of medical diseases in men. Recent studies in men from Europe and the USA have focused on cancer risk, demonstrating links between malignancies and offspring numbers or fertility in men (Moller and Skakkebaek, 1999; Giwercman et al., 2005; Jorgensen et al., 2008; Walsh et al., 2010; Eisenberg et al., 2011). As ~35% of the male human genome is involved in reproduction, it is conceivable that other health ailments, such as cardiovascular disease, may also be linked to defects in fertility (Skakkebaek et al., 2001; Matzuk and Lamb, 2008).

To date, most of the studies examining links between fecundity and cardiovascular health have been restricted to women, while few studies have explored the relationship between offspring number and cardiovascular disease in men (Colditz et al., 1987; Green et al., 1988; Palmer et al., 1992; Ness et al., 1993; Koski-Rahikkala et al., 2006). As such, the association between fatherhood and cardiovascular disease remains uncertain (Dekker and Schouten, 1993; Lawlor et al., 2003). Biologic plausibility for such a relationship exists through hormonal pathways as impaired androgen states have been linked to infertility and cardiovascular mortality (Andersson et al., 2004; Khaw et al., 2007). However, as offspring number is related to socioeconomic position, social determinants may also have an impact in the observed associations given that many cardiovascular risk factors (i.e. activity level, alcohol and tobacco use and BMI) are also related to sociodemographic factors.
Using a prospective cohort design, we studied 135 000 US men to determine whether offspring number associates with mortality from cardiovascular disease contracted in the middle age.

Materials and Methods

Study population

In 1995–1996, 3.5 million members of the AARP (American Association of Retired Persons) who were between the ages of 50–71 and living in one of the six states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) or two metropolitan areas (Atlanta, GA and Detroit, MI) were mailed a questionnaire on medical history and lifestyle characteristics to initiate the NIH-AARP Diet and Health Study (Schatzkin et al., 2001). The AARP is a US-based non-governmental organization and interest group comprised people aged 50 years and over. In all, 567 169 (16.2%) respondents satisfactorily completed the initial survey. In late 1996, a supplementary survey was mailed to those participants who had successfully completed the baseline survey and did not have prostate, breast or colon cancer at baseline. The additional questionnaire asked questions regarding the number of offspring. A final questionnaire was sent to all living participants in the baseline cohort beginning in 2004.

Among the 334 908 individuals who responded to the supplemental questionnaire, we excluded women (n = 138 057), men who had the survey filled out by a proxy (n = 3 967), men with prevalent cardiovascular or cerebrovascular disease (n = 36 910), men with no follow-up (n = 4) and men with missing offspring data (n = 13 108). In addition, men who had never been married (n = 4959) were excluded as reproductive opportunities or desires of such men were difficult to assess as only 2% of this group had children. After these exclusions, there were a total of 137 903 men available for analysis.

Identification of prevalent cardiovascular disease and cardiovascular death

On the baseline questionnaire, individuals were asked: ‘Have you ever been told by a doctor that you had any of the following conditions?’ Heart disease and stroke were among the medical conditions queried, and any participant affirming these conditions was excluded from our analysis. This was done because differences in duration of cardiovascular disease can affect prevalence and, by excluding such men from our analysis, we could estimate the incident risk more accurately. Removing prevalent cardiovascular disease also minimizes the possibility of an effect–cause interaction. However, it has the consequence that the study considers only cardiovascular disease contracted in the study period, i.e. in middle age (>50 years). Deaths were assessed through linkage with the Social Security Administration Death Master File, the National Death Index Plus, cancer registry linkage, questionnaire responses and responses to other mailings with a final evaluation on 31 December 2005. Cardiovascular cause-specific mortality was determined using the International Classification of Diseases, ninth edition.

Assessment of offspring number

Information on offspring number was assessed by self-report. The survey asked: ‘How many sons do you have, both living and deceased? Include blood relatives only’. ‘How many daughters do you have, both living and deceased? Include blood relatives only’. The total offspring number was generated by summing the results of total sons and daughters. Because of low numbers of persons with very high numbers of offspring, we collapsed those with five or more offspring into one category.

Statistical analysis

Each participant accrued follow-up time from the date the supplementary (1996) questionnaire was returned until death, or at the end of the study period, 31 December 2005. Baseline data represent responses to the baseline and supplementary questionnaires. Cox proportional hazards regression was used to estimate the relationship between the offspring number and cardiovascular mortality. The proportional hazards assumption was assessed using log minus log plots and the Schoenfeld test and upheld for all analyses. Poisson regression was used to estimate age-adjusted incidence rates for mortality analysis.

Covariates that have been consistently shown in the literature to affect cardiovascular risk or offspring number were selected for inclusion a priori, including age (continuous), race (categorical: white, black, Hispanic and other), education (categorical: <high school, high school and some college and ≥college), marital status (currently married/formerly married), median household income for zip code of the retiree (continuous), activity level in the last 12 months (categorical: never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week and ≥5 times/week), smoking status (categorical: never, former, and current), alcohol consumption (categorical: 0, 0–4.9, 5–14.9, 15–34.9 and ≥35 g/day), BMI (continuous), diabetes status (dichotomous: Y/N) and self-reported health status (poor/fair/ good/very good/excellent). Linear trend tests were based on ordered categorical variables in the model after replacing each category with the mean of the original variable. Effect modification (i.e. age, current marital status, BMI, diabetes, etc.) was assessed using likelihood-ratio tests with no significant interaction identified. All statistical tests were two sided and P value of <0.05 was considered to be statistically significant. STATA 10 (Statacorp, College Station, TX, USA) was used for all analyses.

Results

Among the 137 903 men available for analysis (mean age 62.7 years, 2.3% Black, 1.7% Hispanic and 1.4% Asian/Pacific Islander/Native American), almost all (92%) were fathers with an overall mean of 2.6 children (Table I). A total of 13 702 men died from any cause, yielding an age-adjusted mortality rate of 11.63 per 1000 person-years. Of these, 3082 (22%) were deaths from cardiovascular disease, yielding an age-adjusted cardiovascular mortality rate of 2.70 per 1000 person-years (Table II).

Before adjustment, hazard ratios demonstrated a U-shaped association with number of offspring, with a nadir in mortality among men with two children (Fig. 1A). After adjustment, however, the shape of this association changed such that excess mortality was observed only at the left-hand side of the distribution (Fig. 1B). Compared with fathers, childless men had a 17% (95% CI: 3–32%) increased risk of cardiovascular death after adjustment (Table II). When childless men were grouped with fathers of only one child, the risk of cardiovascular death was 13% (3–23%) higher than men with two or more children (Table II).

Childless men also had a slightly higher rate of all-cause mortality compared with fathers (7%, 95% CI: 0–13%, Table III). Men with one or no children also had a 5% higher rate of all-cause mortality (95% CI: 1–10%) compared with men with two or more children (Table III). If cardiovascular deaths were eliminated from the analysis, no significant difference based on fatherhood was noted (data not shown).
Discussion

The current study found that childless men have an increased risk of death from cardiovascular disease that developed in the study period compared with fathers after controlling for factors that contribute to cardiovascular disease and are associated with family size. A similar but smaller magnitude of association was present for all-cause mortality. While unadjusted analyses showed U-shaped associations,
after adjustment a threshold effect is seen whereby men with one or no child have a higher risk of mortality.

Our finding of a negative association between offspring number (particularly no and one offspring) and cardiovascular risk is consistent with some, but not all, of the previous reports. Lawlor et al. (2003) examined the relationship of prevalent cardiovascular disease with offspring number in an English population. Similar to the current report, men with no or one child seemed to show higher risks of cardiovascular disease than those with more children; however, the childless men category included 30% single men, which may complicate issues related to reproductive intent or opportunities in this population. It should be noted that a J-shaped relationship between offspring number and cardiovascular disease was seen, whereby men with two to three children had the lowest prevalence. A Swedish study examined the relationship between fatherhood and cardiovascular death and also found childless men at higher risk for death from ischemic heart disease (relative risk 2.0, 95% CI: 1.8–2.2; Ringback Weitoft et al., 2004). Similarly, an Italian group found that infertile men had a higher number of medical co-morbidities than a fertile comparison group (Salonia et al., 2009). In contrast, a Dutch study analyzed the relationship between cardiovascular death and offspring number and found a positive relationship, whereby the risk of cardiovascular death increased with increasing offspring number (Dekker and Schouten, 1993). In this study, a man’s offspring number was assessed by asking his spouse about her own pregnancies and miscarriages. Without an examination of a man’s true reproductive potential, the relationship could only be attributed to socioeconomic or emotional factors. Other investigators have failed to show any relationship between offspring number and cardiovascular disease in men (Ness et al., 1995; Hardy et al., 2007).

Childless men or men with one child likely represent a heterogeneous group, including men with biologic and/or social reasons for limiting family size. By limiting our analysis to only men who had...
been married, reproductive opportunities were partially accounted for. Nevertheless, our sample of childless men includes men who may have decided not to procreate, chose to limit their number of children or had subfertile partners. In the 2002 National Survey of Family Growth, 75% of childless, married men of reproductive age in the USA reported a desire for offspring, suggesting that impaired fertility may play a role in preventing fatherhood status in some portion of this demographic group (Martinez et al., 2006). Some proportion of men with impaired fertility may also have a degree of testicular impairment, which may place them at a relative testosterone-deficient state. As hypogonadism is known to be a risk factor for cardiovascular disease and mortality, such an explanation may link offspring number to cardiovascular death (Khaw et al., 2007; Laughlin et al., 2008).

The association between offspring number and the development of malignancies such as testis or prostate cancer in men is often explained through testicular function (Skakkebaek et al., 2001; Giwercman et al., 2005). As fecundity is known to influence family size, it is possible that men with lower offspring numbers (i.e. childless or one child child) may have impaired fertility (Joffe et al., 2009; Breyer et al., 2010). Using fecundity as a marker for testicular function and androgen production, a relative state of testis failure and androgen deficiency may plausibly be expected to lead to increased risks of testis cancer and breast cancer and lower prostate carcinogenesis.

Androgens also play a role in cardiovascular disease, and while some past reports suggested that high androgen levels increase cardiovascular risk, current data suggest that androgen deficiency increases the risk for cardiovascular disease (Lesko et al., 1993; Simon et al., 1997; Hak et al., 2002). Khaw et al. (2007) showed that cardiovascular and coronary heart mortality declined with increasing serum testosterone levels. Thus, it is possible that a biological cause could also explain both smaller family size and higher cardiovascular disease risk, i.e. the same factors that limited a man’s ability to sire offspring (impaired testicular function) may also increase his risk of cardiovascular disease (impaired androgen state). Indeed, infertile men have lower testosterone levels than their fertile counterparts (Andersson et al., 2004; Meeker et al., 2007).

Several limitations warrant mention. Participants’ reproductive intent, potential and ability of their partners could not be assessed; thus, offspring number is an imperfect surrogate measure of reproductive potential. Offspring number was self-reported and could be inaccurate; however, other studies have established the accuracy of self-reported reproductive histories (Paganini-Hill and Ross, 1982; Harlow and Linet, 1989). It is also conceivable that the relationship between cardiovascular mortality and fatherhood may have resulted from unmeasured confounding or chance alone. Indeed, examining offspring number as a risk factor was not a primary goal when the cohort was assembled. While men had their entire reproductive lives to procreate and develop cardiovascular disease, the present study focused on the incidence of the disease in the middle age (>50 years). Prevalent cardiovascular disease was present in 22% of men otherwise eligible for enrollment and mortality outcomes may have occurred before men had the opportunity for enrollment into the study but after they had sired all their offspring. It is also possible that bias was introduced because the chance of dying before the study or being excluded for prevalent cardiovascular disease differed according to the number of offspring and removed susceptible individuals from the study population. Estimation of the lifetime mortality effect requires study over a greater span of the reproductive years than the average follow-up period of 10.2 years beginning at age 50 provided here. The current methodology could only analyse cardiovascular disease that developed at a relatively advanced age which represents a fraction of in the study population; therefore, it may underestimate the true association between childlessness on cardiovascular mortality.

In addition, parental age at each child’s birth was not known and has been shown in other studies to affect the relationship between health and offspring number (though only modestly for fathers) (Grundy and Kravdal, 2008). How long offspring lived with their fathers was not known, and this may also affect parental health (Ringback Weitoft et al., 2004). Moreover, offspring number may also reflect marital strain which has been shown to be related to cardiovascular mortality (Eaker et al., 2007).

Nevertheless, our study is the largest study to examine the relationship between fatherhood and cardiovascular disease in the USA. With more than 3000 men in our sample dying from cardiovascular disease, and measurements sufficient to control for potential confounding demographic and lifestyle factors, our study helps establish the inverse relationship between offspring number and cardiovascular disease risk. As a man’s fertility potential is often known in early life, our work suggests that the fatherhood status may provide insight into a man’s risk of cardiovascular disease and death later in his life.

This manuscript is dedicated to Arthur Schatzkin.

**Authors’ roles**

A.S., A.H. and Y.P. contributed to study recruitment and data assembly. M.E., Y.P., A.S. and M.P. contributed to data analysis and interpretation. M.E. drafted the manuscript. All authors provided critical revision and final approval of the manuscript.

**Acknowledgements**

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or DOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The
Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, and Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, State of Nevada Department of Health and Human Services. We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

**Funding**

Funding for the NIH-AARP study was through the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD, USA.

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