

HHS Public Access

Author manuscript Andrology. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Andrology. 2022 November; 10(8): 1511–1521. doi:10.1111/andr.13242.

Male personal heat exposures and fecundability: a preconception cohort study

Craig J. McKinnon^a, Dhruv J. Joglekar^a, Elizabeth E. Hatch^a, Kenneth J. Rothman^{a,b}, Amelia K. Wesselink^a, Mary D. Willis^a, Tanran R. Wang^a, Ellen M. Mikkelsen^c, Michael L. Eisenberg^d, Lauren A. Wise^a

^aDepartment of Epidemiology, Boston University School of Public Health, 715 Albany Street, Boston, Massachusetts 02118

^bRTI International, 3040 East Cornwallis Road, P.O. Box 12194 Research Triangle Park, North Carolina, 27709

^cDepartment of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45 8200 Aarhus N, Denmark.

^dDepartment of Urology and Obstetrics & Gynecology, Stanford University School of Medicine, 291 Campus Drive, Stanford, California

Abstract

Background: Several studies indicate adverse effects of selected heat exposures on semen quality, but few studies have directly evaluated fertility as an endpoint.

Objective: We evaluated prospectively the association between male heat exposures and fecundability, the per-cycle probability of conception.

Materials & Methods: We analyzed data from 3,041 couples residing in the United States or Canada who enrolled in a prospective preconception cohort study (2013–2021). At enrollment, males reported on several heat-related exposures, such as use of saunas, hot baths, seat heaters, and tight-fitting underwear. Pregnancy status was updated on female follow-up questionnaires every 8 weeks until conception or a censoring event (initiation of fertility treatment, cessation of pregnancy attempts, withdrawal, loss to follow-up, or 12 cycles), whichever came first. We used proportional probabilities models to estimate fecundability ratios (FR) and 95% confidence intervals (CI) for the association between heat exposures and fecundability, mutually adjusting for heat exposures and other potential confounders.

Corresponding author: Lauren A. Wise, Department of Epidemiology, Boston University School of Public Health, 715 Albany Street, Boston, MA, 02118, (617) 358-3424, lwise@bu.edu.

Authors' contributions

Lauren A. Wise, Elizabeth E. Hatch, and Kenneth J. Rothman designed the original study. Craig McKinnon, Dhruv Joglekar, Tanran R. Wang, and Lauren Wise carried out the statistical analyses. Craig McKinnon drafted the original paper. All authors contributed to the interpretation and presentation of results, and revised the paper critically for intellectual content. All authors read and approved the final manuscript.

Disclosures

PRESTO has received in-kind donations from Swiss Precision Diagnostics (home pregnancy tests), Kindara.com (fertility app), FertilityFriend.com (fertility app), and Labcorp (for semen kits). Dr. Lauren Wise is a consultant on uterine fibroids and abnormal uterine bleeding for AbbVie.

Results: We observed small inverse associations for hot bath/tub use (3 vs. 0 times/month: FR=0.87, 95% CI: 0.70–1.07) and fever in the 3 months before baseline (FR=0.94, 95% CI: 0.79–1.12; 1 cycle of follow-up: FR=0.84, 95% CI: 0.64–1.11). Little association was found for sauna use, hours of laptop use on one's lap, seat heater use, time spent sitting, and use of tight-fitting underwear. Based on a cumulative heat metric, FRs for 1, 2, 3, and 4 vs. 0 heat exposures were 0.99 (95% CI: 0.87–1.12), 1.03 (95% CI: 0.89–1.19), 0.94 (95% CI: 0.74–1.19), and 0.77 (95% CI: 0.50–1.17), respectively. Associations were stronger among men aged 30 years (4 vs. 0 heat exposures: FR=0.60, 95% CI: 0.34–1.04).

Conclusion: Male use of hot tubs/baths and fever showed weak inverse associations with fecundability. Cumulative exposure to multiple heat sources was associated with a moderate reduction in fecundability, particularly among males aged 30 years.

Keywords

Cohort studies; fertility; preconception; male; heat exposure

INTRODUCTION

The World Health Organization defines infertility as the inability to achieve clinical pregnancy after 12 months of regular unprotected intercourse.¹ About 15% of North American couples experience infertility,² and U.S. health care costs for infertility treatment exceed \$5.5 billion.³ These costs are expected to increase as the percentage of females aged 22–44 years using assisted reproductive technologies (ART) continues to increase (e.g., from 0.1% in 1995 to 0.6% in 2006–2010).⁴ Infertility is associated with psychological and financial hardship for affected couples,^{5,6} and ART use has been associated with adverse pregnancy outcomes.^{7–11} Thus, elucidating modifiable determinants of infertility is an important public health goal.

Male factors contribute to 30–50% of infertility diagnoses.^{12,13} A recent review of 185 studies of 42,935 men provided evidence of a decline in sperm concentration in Western countries over the last 40 years (1973–2011).¹⁴ The reasons for this decline, however, are not clear. One factor may be the extent to which sperm concentration is influenced by testicular heat exposures, such as long hours of sitting, use of laptops on one's lap, use of seat heaters, exposure to wet heat, and wearing restrictive clothing. In a study of mice, testicular hyperthermia inhibited spermatogenesis, with apoptosis being observed after 20 minutes of exposure to 43°C, but not after shorter exposure to 39°C.¹⁵ Thus, there may be a threshold effect of heat exposure, though this threshold could be as small as a 1–2°C elevation and seems likely to depend on duration, intensity, and frequency of exposure.¹⁶ Testicular hyperthermia may also damage DNA integrity. In animal studies, DNA damage of sperm was detected as early as a few days after hyperthermia and persisted for weeks after exposure.^{17–19}

Human studies also provide evidence for harmful effects of heat exposure on semen parameters. Occupational exposure to high temperatures has been associated with morphologically-abnormal sperm and impaired motility,²⁰ and increased scrotal temperature has been associated with reduced sperm concentration.²¹ In two randomized clinical studies,

scrotal hyperthermia was associated with reduced sperm DNA integrity and increased sperm apoptosis.^{22,23} Despite these associations between heat exposures and semen quality, it is unclear which heat sources, if any, affect sperm enough to influence fecundability. Direct evaluation of fecundability is important,^{12,24–26} and only two papers have examined heat-related factors with fecundability itself as an endpoint.^{27,28}

We evaluated the extent to which fecundability is associated with selected male heat-related exposures, including use of saunas, hot tubs, or hot baths; use of tight-fitting underwear; time spent sitting; use of car seat heaters; use of a laptop computer on one's lap; and fever.

MATERIALS AND METHODS

Study population.

Pregnancy Study Online (PRESTO) is an ongoing web-based preconception cohort study.²⁹ Female-identified individuals aged 21–45 years residing in the U.S. or Canada, who were in a stable relationship with a male-identified partner, and who were not using contraception or fertility treatment were eligible for participation. The study was approved by the Institutional Review Board at Boston Medical Center, and online informed consent was obtained from all participants.

Study procedures.

Female participants completed an online baseline questionnaire with items on demographics, behavioral factors, medical and reproductive history, and medication use. After completion of the baseline questionnaire, females were given the option to invite their male partners to participate. Males aged 21 years were eligible. Male participation involved completion of a single questionnaire similar to the female baseline questionnaire. Females completed follow-up questionnaires every 8 weeks until reported pregnancy or for up to 12 months, whichever came first.

Exclusions.

From June 2013 through August 2021, 15,592 eligible females completed the baseline questionnaire. We excluded 163 females whose baseline date of last menstrual period (LMP) was >6 months before study entry, 34 females with missing/implausible LMP data, and 39 females who finished their baseline questionnaire >60 days after completing the eligibility screener. We then excluded 3,079 females who had been trying to conceive for more than 6 cycles at enrollment, to reduce potential for differential exposure misclassification (*i.e.*, subfertility causing changes in behavior). Of the 12,277 remaining females, 6,572 (54%) invited their male partners to participate, and 3,041 males (46%) enrolled. Female participants were more likely to invite their partners if they identified as non-Hispanic white, were married, and they or their partners were more educated. Male partners were more likely to enroll if they identified as non-Hispanic white, were younger, and they or their partners were more educated.²⁹

Assessment of exposure characteristics.

On the baseline questionnaire, we ascertained habitual heat-related exposures including: daily average time using laptops on one's lap (none, 0.5, 1, 2, 3, ..., 24 hours/day), average frequency of "hot sauna" use in the last six months (never, 1–2, 3–4, 5–9, 10 times/month), average frequency of taking "hot baths" or sitting in a "hot tub" in the last six months (never, 1–2, 3–4, 5–9, 10 times/month), time spent during the wintertime "traveling in the car with the seat heaters on in your seat" (0–2, 3–5, 6–10, 11–15, 16–20, >20 hours/week), type of underwear usually worn (none, loose boxer shorts, slim-fitting briefs or boxers, alternate loose boxer shorts and slim-fitting briefs/boxers), and daily average time spent during the last year "sitting or lying down watching TV or videos" (0, <1, 1, 2, 3–4, 5–6, 7 hours/day) or "other sitting (such as driving, working at a computer, or reading)" (0, <1, 1, 2, 3–4, 5–6, 7 hours/day). We also queried participants about the number of fevers >100 degrees Fahrenheit they had experienced in the last 3 months (none, 1, 2 times).

Since each of these heat exposures does not necessarily occur on their own, we developed a metric to derive a cumulative heat exposure variable. We dichotomized each heat variable at an arbitrarily-determined "high" cut point, given the lack of clinically meaningful cut points in the literature. We then summed the number of variables for which the participant was in the "high" category. We chose the following cut points to denote "high" exposure: laptop use 5 hours/day, sauna use 3 times/month, hot tub/bath use 3 times/month, any use of tight-fitting underwear, sitting 10 hours per day, any fever (in the previous 3 months), and seat heater use 3 hours/week. Given these cut points were arbitrarily chosen, we also performed sensitivity analyses based on less stringent cut points.

Assessment of pregnancy and cycles at risk.

At baseline, females reported their LMP date, usual menstrual cycle length, and the number of cycles of pregnancy attempt. On each follow-up questionnaire, they reported their most recent LMP date and whether they had conceived since the previous questionnaire. Total discrete menstrual cycles at risk were calculated as follows: menstrual cycles of attempt time at study entry + [(LMP from most recent follow-up questionnaire - LMP from baseline questionnaire)/usual menstrual cycle length] +1. Couples contributed observed cycles of attempt time to the analysis from baseline until reported conception, initiation of fertility treatment, cessation of trying to conceive, loss to follow-up, withdrawal, or 12 cycles, whichever came first.

Assessment of covariates.

On their respective baseline questionnaires, male and female participants reported their age, race/ethnicity, education, height, and weight. The male baseline questionnaire collected data on physical activity, alcohol intake, smoking history, sleep duration, employment status, including hours worked per week, having previously fathered a child, and infertility history. Household income and frequency of intercourse were ascertained from the female baseline questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Total Metabolic Equivalents of Task (MET) of physical activity were calculated by multiplying the average number of hours per week engaged

in various activities by metabolic equivalents estimated from the Compendium of Physical Activities.^{30,31}

Imputation of missing data.

We used fully conditional specification methods to conduct multiple imputations for missing data on outcome, exposure, and covariates. We generated twenty imputation data sets and combined point estimates and standard errors from each data set using Rubin's rule. For the 206 couples (6.8%) with no follow-up data, we assigned them one cycle of follow-up and multiply-imputed their pregnancy status (yes or no). Data on fever were missing for 21% of men because it was added to the male baseline questionnaire in January 29, 2015, 18 months after the study was launched. Missingness for other variables ranged from <0.1% (age, alcohol, smoking, physical activity) to 2% (fathered a child). We used the weighted copy method to improve convergence of the regression model.³⁶ All analyses were performed in SAS version 9.4.³⁷

Data analysis.

We used an Andersen-Gill data structure, with one observation per observed menstrual cycle, to account for variation in attempt time at study entry and left truncation.³² We used proportional probabilities regression models³³ to estimate fecundability ratios (FR) and 95% confidence intervals (CI) for the association between heat exposure measures and fecundability. The FR represents the ratio of the per-cycle probability of conception (*i.e.*, fecundability) in each exposure category compared with the reference category. The proportional probabilities model incorporates the baseline decline in fecundability over time.³²

We selected potential confounders *a priori* based on the available literature by assessment of a directed acyclic graph. Results were adjusted for covariates ascertained at baseline, including male age (<25, 25–29, 30–34, 35 years), annual household income (<50,000, 50,000–99,999, 100,000–149,999, 150,000 US dollars), race/ethnicity (White/ non-Hispanic vs. other), highest education achieved (less than high school, high school, some college, college, graduate studies), total METs (continuous), alcohol consumption (0, 1–6, 7–13, 14 drinks/week), BMI (<25, 25–29, 30 kg/m²), cigarette smoking (never, past, current), sleep duration (<6, 6, 7, 8, 9 hours/day), currently employed (yes vs. no), hours of employment (<30, 30–49, 50 hours/week), and previously fathered a child (yes vs. no). In multivariable models, heat exposures were mutually adjusted for each other. In additional multivariable analyses, we adjusted for female age (<25, 25–29, 30–34, 35 years), female BMI (<25, 25–29, 30 kg/m²), and intercourse frequency (<1/week, 1/week, <1/day, 1/day).

Given that the male exposure data were collected on a single baseline questionnaire, we restricted analyses to the first 3 cycles of follow-up to reduce the effect of changes in heat exposures after enrollment. Spermatogenesis takes on average 72 days from start to finish,³⁴ which is close in length to 3 cycles of follow-up (~84 days). If a participant changed his behavior in response to subfertility, the effects of that change would not be seen until the 4th cycle of follow-up at the earliest. Therefore, restricting to the first three

cycles of follow-up should reduce misclassification of exposure due to behavior change. This method of restricting follow-up time has been shown to reduce attenuation of FRs in time to pregnancy studies.³⁵ Finally, given that fever is not a habitual exposure like all other heat exposures we evaluated, we further restricted the fever analyses to the first cycle of follow-up.

We analyzed the cumulative heat exposure variable as continuous and categorical (0, 1, 2, 3, and 4), and we adjusted for the same set of variables above. In secondary analyses, we restricted to couples with pregnancy attempt times of <3 cycles to assess potential for reverse causation bias. We also stratified by variables that could plausibly modify the association between heat-related exposures and fecundability, such as male age (<30 vs. 30 years) and history of infertility in the male partner. Older male age is inversely associated with fertility in some studies and we reasoned that older males may be more susceptible to the effects of heat.

RESULTS

A total of 3,041 couples contributed 1,335 pregnancies during 6,943 observed menstrual cycles of attempt time. Of the male participants analyzed, median age at baseline was 31 years (interquartile range: 28–35 years), 68% reported 16 years of education, 15% reported household incomes <\$50,000, 45% had previously fathered a child, 84% reported identifying as white non-Hispanic, 28% reported BMIs 30 kg/m², 11% reported current cigarette smoking, and 70% had <3 cycles of pregnancy attempt time at enrollment. At baseline, 13.2% of men reported laptop use on their laps for 3 hours on average each day, 6.3% of men reported sauna use, and 7.3% of men took hot baths/tubs 3 times per month (Table 1). Additionally, 29.3% of men reported use of seat heaters during wintertime, 63.3% reported wearing slim fitting briefs/boxers, 17.9% reported sitting for 10 hours per day, and 12.0% reported at least one fever greater than 100°F within the three months before enrollment (Table 1).

Baseline characteristics associated with the largest number of heat exposures included: BMI, which was positively associated with sauna use, time spent sitting, and fever; having previously fathered a child, which was positively associated with fever and use of saunas and hot baths/tubs; physical activity, which was positively associated with use of saunas and hot baths/tubs, and inversely associated with time spent sitting; household income, which was positively associated with seat heater use and time spent sitting, and inversely associated with fever; and alcohol consumption, which was positively associated with sauna use and inversely associated with fever and wearing slim-fitting underwear. Several personal heat exposures were positively associated with each other (e.g., use of saunas and hot baths/tubs; time spent sitting and laptop use) (Table 1).

As shown in Table 2, use of hot tubs/baths (3/month vs. none) was associated with slightly reduced fecundability (FR=0.87, 95% CI: 0.70–1.07) and there was evidence of a monotonic inverse association. Fecundability was not appreciably associated with laptop use on one's lap (5 vs. <1 hour/day: FR=0.99, 95% CI: 0.82–1.19), sauna use (3 saunas/month vs. none: FR=1.04, 95% CI: 0.73–1.48), seat heater use during the winter months (3 hours/

week vs. none: FR=0.97, 95% CI: 0.83-1.14), use of tight-fitting underwear (slim-fitting briefs/boxers vs. loose boxers/no underwear: FR=1.04, 95% CI: 0.93-1.16), or sitting (10 vs. <5 hours/day: FR=0.94, 95% CI: 0.80-1.10). The FR for a fever episode in the 3 months before baseline was 0.94 (95% CI: 0.79-1.12). Given that fever is not a habitual exposure like the other heat-related exposures under study, we further restricted the analysis to the first cycle of follow-up; the corresponding FR was stronger (0.84, 95% CI: 0.64-1.11). Further adjustment for female partner's age, female partner's BMI, and intercourse frequency did not substantively alter the results. Associations for use of hot tubs/baths and fever were slightly stronger among males aged 30 years (Supplemental Table 1).

In the cumulative heat exposure variable, FRs for 1, 2, 3, and 4 heat factors were 0.99 (95% CI: 0.87–1.12), 1.03 (95% CI: 0.89–1.19), 0.94 (95% CI: 0.74–1.19), and 0.77 (95% CI: 0.50–1.17), respectively (Table 2). These associations did not change appreciably after restricting to 1) couples with fewer than 3 cycles of attempt time at enrollment and 2) male partners without a history of infertility (Table 3). However, inverse associations were stronger among men aged 30 years: for 1, 2, 3, and 4 heat factors, the FRs were 0.90 (95% CI: 0.77–1.05), 0.89 (95% CI: 0.74–1.07), 0.85 (95% CI: 0.64–1.14), and 0.60 (95% CI: 0.34–1.04), respectively. Results from the analyses not restricted to the first 3 cycles of follow-up generally yielded attenuated FR estimates (Supplemental Table 2). Finally, the cumulative heat exposure associations were attenuated after fever was removed as a heat factor (Tables 2 and 3); however, there was still some evidence, albeit imprecise, of a slight inverse association for exposure to 4 heat factors among males aged 30 years (FR=0.76, 0.38–1.52) (Table 3).

DISCUSSION

In this preconception cohort study, we found small associations for selected individual heat factors and some evidence of a threshold effect for cumulative exposure to multiple heat factors. Fecundability tended to decrease slightly after exposure to 3 heat factors. Associations were somewhat stronger among men aged 30 years. When assessing each heat factor individually, we found small reductions in fecundability with hot tub/bath use (3 times/month) and fever. The inverse association with fever was strongest when restricting to the first cycle of follow-up. We found little evidence of an association between fecundability and sauna use, laptop use on one's lap, type of underwear worn, seat heater use, or time spent sitting. Additional control for known or suspected confounders (e.g., alcohol consumption, education) and female covariates made little difference in these associations.

In the cumulative heat exposure analysis, men exposed to three heat factors had slightly lower fecundability than those exposed to none; this association was stronger for those exposed to four or more heat factors. This heat effect appeared to be stronger among males aged 30 years. Our cumulative heat exposure metric, however, is not a standard or validated measure, and our selection of what constituted high exposure for each component of the measure was somewhat arbitrary. While limited in its utility, this metric allows us to better understand the influence of multiple heat exposures on male fertility, and future research can parse the impact of this mixture of exposures in more detail. Removal of fever from the heat

Our equivocal findings for sauna use conflict with some studies reporting that sauna use can impair spermatogenesis,^{38,39} but are consistent with other studies showing little effect.^{40–43} Differences in results across studies could relate in part to differences in the timing, duration, and frequency of exposure, or could be due to chance. In contrast, our results regarding the use of hot baths agree with previous studies indicating an association between use of hot baths and decreased sperm concentration.^{22,23} These results also align with a study reporting substantial improvements in sperm motility among men assigned to an intervention involving cessation of wet heat exposure.⁴⁴

Previous studies have reported an association between time spent sitting and increased scrotal temperatures.^{29,45–48} Additional studies have also reported that seat heater use further increased scrotal temperatures compared with sitting alone.^{49,50} In our study, however, neither sitting alone nor seat heater use was associated with decreased fecundability. The latter analyses may have been misclassified based on timing of enrollment (e.g., in the summer months) or based on geographic region (e.g., if participants lived in hotter areas of the United States or Canada where seat heaters are not used); in both of these scenarios, we would expect attenuation of our estimates towards the null.

The lack of association between laptop use on one's lap and fecundability conflicts with several earlier studies indicating that laptop use can harm spermatogenesis via radiation or direct heat stress to the scrotum.^{51,52} Older generations of laptops have been shown to increase testicular heat exposure more than just sitting alone and they have been associated with sperm damage.⁵³ However, PRESTO participants may be more likely to use newer laptop models that contain solid-state drives and other power improvements associated with cooler operating temperatures that are not expected to appreciably influence testicular temperatures.

We found little association between underwear type and fecundability. Previous studies have been mixed on this topic,^{28,46,54–56} with one study reporting that use of tighterfitting underwear was associated with higher scrotal temperatures.⁵⁴ The temperature difference in those studies was small (average 35.8°C/96.4°F for tight-fitting underwear, 35.5°C/95.9°F for boxer shorts, and 35.2°C/95.4°F for no underwear). In other studies, tight-fitting underwear was associated with lower sperm concentration,⁵⁵ indicating neck and tail abnormalities and sperm DNA damage. One study reported no appreciable difference between scrotal temperature or semen parameters comparing tight-fitting underwear with boxer shorts.⁵⁶ Our study agrees with a previous prospective preconception cohort study, of similar design to PRESTO, in which wearing tight-fitting underwear was adversely associated with semen quality. Thus, poorer semen quality may not translate into observable differences in fecundity.

Fevers can increase overall body temperature, including scrotal temperature. Fever above 100°F within three months before baseline was associated with slightly reduced

fecundability. This association was stronger when restricted to the first cycle of follow-up, an important finding for an exposure such as fever, which is time-limited, unlike the other heat exposures. Though we specified the body temperature at which we defined fever (>100°F), we did not query participants about what specific body temperature they experienced during these episodes, nor did we ask about fever duration, cause of the fever, or which treatments were used to treat any fever-associated illness. Previous studies based on extremely small numbers have shown decrements in sperm quality related to fever duration, ⁵⁸ with longer durations of fever being associated with reduced sperm count and motility, and greater DNA damage.^{59,60} We acknowledge that fever is not a modifiable risk factor, nor is it an "external" exposure like the other exposures that we considered, and thus its inclusion as a personal (or habitual) heat factor in the heat metric may be debated. For this reason, we repeated the analyses without fever in our heat metric and results showed similar findings in general.

Although PRESTO is one of the largest preconception cohort studies of male reproductive health worldwide, male participation was relatively low (i.e., 54% of females invited their partners to participate, and 46% of males invited actually enrolled, yielding fewer than 25% of males enrolled). Given the prospective study design, potential for selection bias was reduced because participants were unaware of their future fecundability; thus, it was unlikely for participation to be related to both exposure *and* outcome. Moreover, findings from other prospective cohort studies^{61,62,63} indicate that even when there are large differences in the baseline characteristics between participants and non-participants in a prospective cohort study, such differences have little influence on the estimated measures of association. Nevertheless, we cannot rule out the possibility that selection bias influenced study results, nor can we claim that our results extend to a broader population of couples at risk of pregnancy.

We relied on self-reported data of typical heat exposure and there were differences in the time frame during which each heat exposure was assessed (e.g., past 6 months for use of saunas or hot baths/tubs vs. past year for hours of sitting). We assessed heat exposures only once, at study enrollment. In addition, we may have missed other relevant heat exposures (e.g., occupational exposures). While many of the heat exposures under study are considered habitual, once a couple starts to experience difficulty conceiving, males might change behaviors to those perceived as less risky (e.g., discontinue use of hot tubs/baths). To reduce this potential bias, we restricted analysis to the first three cycles of follow-up; as expected, results were slightly stronger than analyses based on complete follow-up.³⁵ In addition, restrictions based on attempt time at study entry produced little change in the results. Any resulting exposure misclassification is expected to be non-differential with respect to fecundability given the prospective study design. Thus, our results are likely to be attenuated.

Our study differed from previous studies of heat exposures in various ways: we enrolled men during the preconception period and evaluated heat exposures prospectively relative to the outcome; we did not assess semen quality^{12,24–26} but rather a more clinically-relevant outcome: fecundability; we considered the individual and cumulative effects of several heat-related exposures; we controlled for a wider range of potential confounders measured in

Page 10

both partners; and, at enrollment, participants were attempting spontaneous conception and were not using fertility treatments, thus the cohort represented couples along the full fertility spectrum.

In this preconception cohort study, we found small inverse associations for hot tub/bath use and fever, but not other heat-related factors such as sauna use, seat heater use, tight-fitting underwear use, laptop use, and extended periods of sitting. Additionally, we found evidence of an effect for cumulative exposure to multiple heat-related factors but only after exposure to at least three heat-related factors. These associations appeared to be slightly stronger among older men who might be more sensitive to the effects of heat. An overall harmful effect of heat exposure on fecundability is biologically plausible based on epidemiologic studies showing associations between high temperatures and impaired semen quality.^{20–23} Our direct evaluation of fecundability in this manuscript makes a contribution to the sparse literature evaluating fertility itself as an endpoint.^{27,28} Given that there is no literature with which to compare our results indicating stronger effects of heat exposures among older men, replication of these results in future studies may be worthwhile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We acknowledge the contributions of PRESTO participants and staff. We thank Michael Bairos for technical support in developing the study's web-based infrastructure, and Paul Turek for his contributions to the dissertation work on which this manuscript was based. This work was supported by National Institutes of Health (Grants R01-HD086742, R03-HD090315, R21-HD072326).

REFERENCES

- Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID, Simpson JL, van der Poel S. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril. 2017;108(3):393–406. [PubMed: 28760517]
- Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, Buck Louis GM. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril. 2013;99(5):1324–1331. [PubMed: 23290741]
- Macaluso M, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A, Berman SM, Wang RY, Farr SL, Pollack LA. A public health focus on infertility prevention, detection, and management. Fertil Steril. 2010;93(1):16.e1–10. [PubMed: 18992879]
- Stephen EH, Chandra A, King RB. Supply of and demand for assisted reproductive technologies in the United States: clinic- and population-based data, 1995–2010. Fertil Steril. 2016;105(2):451–458. [PubMed: 26597629]
- Kee BS, Jung BJ, Lee SH. A study on psychological strain in IVF patients. J Assist Reprod Genet. 2000;17(8):445–448. [PubMed: 11062855]
- 6. Cousineau TM, Domar AD. Psychological impact of infertility. Best Pract Res Clin Obstet Gynaecol. 2007;21(2):293–308. [PubMed: 17241818]
- Bay B, Mortensen EL, Kesmodel US. Assisted reproduction and child neurodevelopmental outcomes: a systematic review. Fertil Steril. 2013;100(3):844–853. [PubMed: 23810272]
- Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. Hum Reprod Update. 2013;19(4):330–353. [PubMed: 23449641]

- Qin J, Liu X, Sheng X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancyrelated complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies. Fertil Steril. 2016;105(1):73–76. [PubMed: 26453266]
- Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Infertility, assisted reproductive technology, and adverse pregnancy outcomes: executive summary of a National Institute of Child Health and Human Development workshop. Obstet Gynecol. 2007;109(4):967–977. [PubMed: 17400861]
- Kettner LO, Henriksen TB, Bay B, Ramlau-Hansen CH, Kesmodel US. Assisted reproductive technology and somatic morbidity in childhood: a systematic review. Fertil Steril. 2015;103(3):707–719. [PubMed: 25624193]
- 12. Irvine DS. Epidemiology and aetiology of male infertility. Hum Reprod. 1998;13 Suppl 1:33-44.
- Zhang Y, Xiao F, Lu S, Song J, Zhang C, Li J, Gu K, Lan A, Lv B, Zhang R, Mo F, Jiang G, Zhang X, Yang X. Research trends and perspectives of male infertility: a bibliometric analysis of 20 years of scientific literature. Andrology. 2016;4(6):990–1001. [PubMed: 27389996]
- Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Mindlis I, Pinotti R, Swan SH. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update. 2017;23(6):646–659. [PubMed: 28981654]
- Rockett JC, Mapp FL, Garges JB, Luft JC, Mori C, Dix DJ. Effects of hyperthermia on spermatogenesis, apoptosis, gene expression, and fertility in adult male mice. Biol Reprod. 2001;65(1):229–39. [PubMed: 11420244]
- Morgentaler A, Stahl BC, Yin Y. Testis and temperature: an historical, clinical, and research perspective. J Androl. 1999;20(2):189–95. [PubMed: 10232653]
- 17. Banks S, King SA, Irvine DS, Saunders PTK. Impact of a mild scrotal heat stress on DNA integrity in murine spermatozoa. Reproduction. 2005;129(4):505–14. [PubMed: 15798026]
- Paul C, Murray AA, Spears N, Saunders PTK. A single, mild, transient scrotal heat stress causes DNA damage, subfertility and impairs formation of blastocysts in mice. Reproduction. 2008. Jul;136(1):73–84. [PubMed: 18390691]
- Paul C, Teng S, Saunders PT. A single, mild, transient scrotal heat stress causes hypoxia and oxidative stress in mouse testes, which induces germ cell death. Biol Reprod. 2009;80(5):913–9. [PubMed: 19144962]
- 20. Dada R, Gupta NP, Kucheria K. Spermatogenic arrest in men with testicular hyperthermia. Teratog Carcinog Mutagen. 2003;Suppl 1:235–43. [PubMed: 12616614]
- Hjollund NH, Bonde JP, Jensen TK, Olsen J. Diurnal scrotal skin temperature and semen quality. The Danish First Pregnancy Planner Study Team. Int J Androl. 2000;23(5):309–318. [PubMed: 11012789]
- 22. Rao M, Xia W, Yang J, Hu LX, Hu SF, Lei H, Wu YQ, Zhu CH. Transient scrotal hyperthermia affects human sperm DNA integrity, sperm apoptosis, and sperm protein expression. Andrology. 2016;4(6):1054–1063. [PubMed: 27410176]
- Rao M, Zhao XL, Yang J, Hu SF, Lei H, Xia W, Zhu CH. Effect of transient scrotal hyperthermia on sperm parameters, seminal plasma biochemical markers, and oxidative stress in men. Asian J Androl. 2015 Jul-Aug;17(4):668–75. [PubMed: 25652627]
- 24. Bonde JP, Ernst E, Jensen TK, Hjollund NH, Kolstad H, Henriksen TB, Scheike T, Giwercman A, Olsen J, Skakkebaek NE. Relation between semen quality and fertility: A population-based study of 430 first-pregnancy planners. Lancet. 1998;352(9135):1172–7. [PubMed: 9777833]
- 25. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney A, Lynch CD, Kim S, Maisog JM, Gore-Langton R, Eisenberg ML, Chen Z. Semen quality and time to pregnancy: the Longitudinal Investigation of Fertility and the Environment Study. Fertil Steril. 2014;101(2):453–62. [PubMed: 24239161]
- Loft S, Kold-Jensen T, Hjollund NH, Giwercman A, Gyllemborg J, Ernst E, Olsen J, Scheike T, Poulsen HE, Bonde JP. Oxidative DNA damage in human sperm influences time to pregnancy. Hum Reprod. 2003;18(6):1265–1272. [PubMed: 12773457]
- Sapra KJ, Eisenberg ML, Kim S, Chen Z, Buck Louis GM. Choice of underwear and male fecundity in a preconception cohort of couples. Andrology. 2016;4(3):500–8. [PubMed: 26939021]

- Figa-Talamanca I, Cini C, Varricchio GC, et al. Effects of prolonged autovehicle driving on male reproduction function: a study among taxi drivers. Am J Ind Med. 1996;30(6):750–758. [PubMed: 8914722]
- Wise LA, Rothman KJ, Mikkelsen EM, Stanford JB, Wesselink AK, McKinnon C, Gruschow SM, Horgan CE, Wiley AS, Hahn KA, Sørensen HT, Hatch EE. Design and Conduct of an Internet-Based Preconception Cohort Study in North America: Pregnancy Study Online. Paediatr Perinat Epidemiol. 2015;29(4):360–71. [PubMed: 26111445]
- 30. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 Suppl):S498–504. [PubMed: 10993420]
- McKinnon CJ, Hatch EE, Rothman KJ, Mikkelsen EM, Wesselink AK, Hahn KA, Wise LA. Body mass index, physical activity and fecundability in a North American preconception cohort study. Fertil Steril. 2016;106(2):451–9. [PubMed: 27125230]
- 32. Therneau T, Grambsch P. Modeling Survival Data: Extending the Cox Model. New York, NY: Springer-Verlag; 2000.
- 33. Weinberg CR, Wilcox AJ, Baird DD. Reduced fecundability in women with prenatal exposure to cigarette smoking. Am J Epidemiol. 1989;129(5):1072–8. [PubMed: 2705427]
- Misell LM, Holochwost D, Boban D, Santi N, Shefi S, Hellerstein MK, Turek PJ. A stable isotope-mass spectrometric method for measuring human spermatogenesis kinetics in vivo. J Urol. 2006;175(1):242–6; discussion 246. [PubMed: 16406920]
- Eijkemans MJC, Leridon H, Keiding N, Slama R. A systematic comparison of designs to study human fecundity. Epidemiology. 2019;30(1):120–129. [PubMed: 30198936]
- Deddens JA, Petersen MR. Approaches for estimating prevalence ratios. Occup Environ Med. 2008;65(7):481,501–506. [PubMed: 18562687]
- 37. SAS. The SAS Institute, Cary, NC. Version 9.4, 2014.
- Garolla A, Torino M, Sartini B, Cosci I, Patassini C, Carraro U, Foresta C. Seminal and molecular evidence that sauna exposure affects human spermatogenesis. Hum Reprod. 2013;28(4):877–85. [PubMed: 23411620]
- Saikhun J, Kitiyanant Y, Vanadurongwan V, Pavasuthipaisit K. Effects of sauna on sperm movement characteristics of normal men measured by computer-assisted sperm analysis. Int J Androl. 1998;21(6):358–63. [PubMed: 9972494]
- 40. Jung A, Schuppe HC. Influence of genital heat stress on semen quality in humans. Andrologia. 2007;39(6):203–15. [PubMed: 18076419]
- 41. Procope BJ. Effect of repeated increase of body temperature on human sperm cells. Int J Fertil. 1965;10(4):333–339. [PubMed: 5891617]
- 42. Brown-Woodman PDC, Post EJ, Gass GC, White IG. The effect of a single sauna exposure on spermatozoa. Arch Androl. 1984;12(1):9–15.
- 43. Jurewicz J, Radwan M, Sobala W, Ligocka D, Radwan P, Bochenek M, Hanke W. Lifestyle and semen quality: role of modifiable risk factors. Syst Biol Reprod Med. 2014;60(1):43–51. [PubMed: 24074254]
- Shefi S, Tarapore PE, Walsh TJ, Croughan M, Turek PJ. Wet heat exposure: A potentially reversible cause of low semen quality in infertile men. Int Braz J Urol. 2007;33(1):50–6. [PubMed: 17335598]
- 45. Brindley GS. Deep scrotal temperature and the effect on it of clothing, air temperature, activity, posture and paraplegia. Br J Urol. 1982;54(1):49–55. [PubMed: 7059758]
- Hjollund NHI, Storgaard L, Ernst E, Bonde JP, Olsen J. The relation between daily activities and scrotal temperature. Reprod Toxicol. 2002;16(3):209–14. [PubMed: 12128093]
- 47. Bujan L, Daudin M, Charlet JP, Thonneau P, Mieusset R. Increase in scrotal temperature in car drivers. Hum Reprod. 2000;15(6):1355–7. [PubMed: 10831568]
- Bigelow PL, Jarrell J, Young MR, Keefe TJ, Love EJ. Association of semen quality and occupational factors: comparison of case-control analysis and analysis of continuous variables. Fertil Steril. 1998;69(1):11–8. [PubMed: 9457925]

- 49. Song GS, Ju TS. Changes in the scrotal temperature of subjects in a sedentary posture over a heated floor. Int J Androl. 2006;29(4):446–57. [PubMed: 16893399]
- 50. Jung A, Strauss P, Lindner HJ, Schuppe HC. Influence of heating car seats on scrotal temperature. Fertil Steril. 2008;90(2):335–9. [PubMed: 17919605]
- 51. Dore J-F, Chignol M-C. Laptop computers with Wi-Fi decrease human sperm motility and increase sperm DNA fragmentation. Fertil Steril. 2012;97(4):e12; author reply e13. [PubMed: 22306709]
- Choy JT, Brannigan RE, Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil Steril. 2012;97(1):39–45.e2. [PubMed: 22112647]
- 53. Sheynkin Y, Jung M, Yoo P, Schulsinger D, Komaroff E. Increase in scrotal temperature in laptop computer users. Hum Reprod. 2005;20(2):452–5. [PubMed: 15591087]
- 54. Jung A, Leonhardt F, Schill WB, Schuppe HC. Influence of the type of undertrousers and physical activity on scrotal temperature. Hum Reprod. 2005;20(4):1022–7. [PubMed: 15618251]
- 55. Tiemessen CH, Evers JL, Bots RS. Tight-fitting underwear and sperm quality. Lancet. 1996;347(9018):1844–1845.
- Munkelwitz R, Gilbert BR. Are boxer shorts really better? A critical analysis of the role of underwear type in male subfertility. J Urol. 1998;160(4):1329–33. [PubMed: 9751347]
- Minguez-Alarcon L, Gaskins AJ, Chiu Y-H, et al. Type of underwear worn and markers of testicular function among men attending a fertility center. Hum Reprod. 2018;33(9):1749–1756. [PubMed: 30102388]
- Carlsen E, Andersson AM, Petersen JH, Skakkebæk NE. History of febrile illness and variation in semen quality. Hum Reprod. 2003;18(10):2089–92. [PubMed: 14507826]
- Evenson DP, Jost LK, Corzett M, Balhorn R. Characteristics of human sperm chromatin structure following an episode of influenza and high fever: a case study. J Androl. 2000;21(5):739–46. [PubMed: 10975421]
- Sergerie M, Mieusset R, Croute F, Daudin M, Bujan L. High risk of temporary alteration of semen parameters after recent acute febrile illness. Fertil Steril. 2007;88(4):970.e1–7. [PubMed: 17434502]
- Hatch EE, Hahn KA, Wise LA, et al. Evaluation of Selection Bias in an Internet-based Study of Pregnancy Planners. Epidemiology. 2016;27(1):98–104. [PubMed: 26484423]
- 62. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? Epidemiology. 2006;17(4):413–418. [PubMed: 16755269]
- 63. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol. 2009;23(6):597–608. [PubMed: 19840297]

Author
· Manuso
cript

Author Manuscript

÷.
<u>e</u>
Tab

-2021
2013-
ESTO),
ne (PRI
ly Onli
cy Stud
Pregnan
osures,]
heat exp
ed male
to selecte
s according 1
articipant
male p
of 3,041
Icteristics
e chara
Baselin

	Laptop use (hours/d	on lap lay)	Sauna ust mon	e (times/ th)	Bath use () month	times/	Seat he	ater use	Type of ı w	ınderwear orn	Time spe (hour	ent sitting s/day)	Fe	ver
Characteristic	Ā	w	Never	ŝ	Never	3	No	Yes	Loose boxer	Slim-fit briefs/ boxer	Ś	10	None	-
Number of Men (%)	2178 (71.6)	247 (8.1)	2849 (93.7)	51 (1.7)	2104 (69.2)	223 (7.3)	2151 (70.7)	890 (29.3)	735 (24.2)	1921 (63.3)	711 (23.4)	544 (17.9)	2675 (88.0)	366 (12.0)
Male age, years (mean)	31.8	32.7	32.0	32.7	32.1	32.6	31.8	32.3	31.9	32.0	31.6	31.3	32.0	31.6
Male education, years (mean)	15.3	15.8	15.4	15.4	15.5	15.4	15.5	15.4	15.6	15.4	14.9	15.5	15.5	15.2
Total MET, hours per week (mean)	32.6	33.5	32.2	48.9	32.1	33.8	32.5	34.0	30.6	33.5	37.3	27.4	32.9	33.8
Cycles of attempt time at study entry (mean)	1.8	1.9	1.8	1.8	1.8	1.9	1.9	1.7	1.8	1.8	1.9	1.9	1.8	1.8
Household income <\$50,000 USD (%)	16.6	10.0	15.5	16.3	14.3	25.1	17.2	10.2	14.5	14.6	20.0	12.7	14.7	19.6
Household income \$150,000 USD (%)	18.2	27.4	20.0	24.6	20.2	15.9	17.5	26.9	19.0	21.4	13.8	23.7	19.8	24.7
White, non-Hispanic (%)	84.9	76.3	84.4	87.9	85.2	77.4	84.8	83.6	84.8	84.3	85.3	83.0	84.6	83.3
Male alcohol intake: None (%)	21.5	18.1	21.6	18.2	22.1	24.1	23.1	15.5	22.1	21.7	20.5	22.8	20.3	27.1
Male alcohol intake: 14 drinks/week (%)	12.9	8.1	11.8	28.8	11.7	13.0	12.8	11.2	13.8	11.2	16.4	13.1	12.4	11.2
Male BMI <25 m/kg ² (%)	31.2	28.7	31.5	27.2	31.1	35.2	31.9	31.4	35.7	29.5	28.5	24.7	32.6	25.8
Male BMI 30 m/kg ² (%)	32.0	33.1	31.2	30.8	32.2	27.2	32.0	28.4	26.8	32.8	30.4	39.1	29.9	38.4
Current smoker (%)	13.2	8.5	12.5	9.6	12.2	11.6	12.7	10.9	11.1	12.6	13.8	11.7	11.9	14.8
Former smoker (%)	16.5	16	15.6	33.1	15.9	24.2	15.1	17.2	12.9	16.2	19.3	15.5	15.2	20.5
Male sleep duration: <6 hours/day (%)	8.7	6.1	8.9	13.8	8.2	12.7	8.6	8.9	10.5	7.6	11.4	9.3	8.4	11.8
Male sleep duration: 9 hours/day (%)	3.7	5.5	3.5	1.5	3.6	1.8	3.7	3.4	3.2	3.9	2.6	6.5	3.8	2.7
Job hours ¹ <30 hours/week (%)	6.5	4.6	6.4	3.6	6.2	10.4	6.9	4.9	5.5	6.3	5.7	4.9	6.3	5.8
Job hours ¹ 50 hours/week (%)	22.7	25.8	23.0	42.7	23.1	24.9	23.9	22.7	21.7	24.4	27.1	22.5	23.1	27.7

±
2
0
2
\geq
b
S
0
Ξ.
¥

	Laptop use (hours/d	on lap 'ay)	Sauna use mont	(times/ 1)	Bath use (i month	times/	Seat h	eater use	Type of 1 w	ınderwear orn	Time sp (hou	ent sitting rs/day)	Fe	ver
Characteristic	\bigtriangledown	w	Never	e	Never	e	No	Yes	Loose boxer	Slim-fit briefs/ boxer	ŝ	10	None	-
Unemployed (%)	5.8	7.5	5.3	2.3	5.0	5.3	5.2	6.0	4.6	5.6	5.0	5.0	5.7	3.7
Laptop use on lap <1 hour/day (%)	I	1	72.8	54.5	73.2	65.7	72.8	70.1	71.7	72.1	78.2	65.0	72.9	66.7
Laptop use on lap 3 hours/day (%)	I	1	5.1	7.8	5.5	2.9	4.9	5.9	3.7	5.9	4.9	6.2	4.8	<i>T.T</i>
Sauna use, never (%)	94.2	87.9	1	ł	97.4	85.1	94.2	91.1	94.7	93.1	93.6	93.9	92.9	95.7
Sauna use, 3/month (%)	1.2	4.5	1	1	0.9	6.7	1.4	2.5	1.2	1.8	2.0	1.7	1.7	1.9
Hot tub/bath use, never (%)	70	62.3	72.1	41.1	I	I	71.7	62.3	73.7	68.3	69.3	71.9	69.2	67.2
Hot tub/bath use, 3/month (%)	6.9	13.5	6.9	29.6	I	I	7.3	8.1	4.9	8.6	8.1	6.6	7.3	8.6
Seat heater use in winter (%)	28	37.1	28.0	43.1	25.9	30.6	I	1	25.2	30.5	29.3	32.6	29.1	25.1
Slim-fit boxer (%)	61.7	64.1	61.6	68.6	61.1	70.6	60.0	65.5	ł	I	61.4	60.9	61.3	65.2
Sit <5 hours/day (%)	24.7	7.5	22.9	31.8	22.9	23.5	22.6	23.5	22.5	22.7	1	I	22.9	21.9
Sit 10 hours/day (%)	16.2	26.6	18.0	16.2	18.5	17	16.9	20.3	18.7	17.7	1	I	17.7	18.9
Fever within 3 months, %	11.1	13.7	12.3	11.6	11.7	13.9	12.6	10.6	11.8	12.6	11.4	13.0	ł	ł
Previously fathered a child, %	42.9	34.0	42.0	34.4	41.1	44.8	41.9	40.2	41.5	41.6	46.9	38.1	40.0	51.8
^a Excludes unemployed														

Exposure	No. of Men	No. of Conceptions	No. of Cycles	Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b	Adjusted FR (95% CI) ^C
Laptop usage on lap, hours/day							
<1	2,178	941	4987	Reference	Reference	Reference	Reference
1	263	127	574	1.17 (0.99–1.37)	1.07 (0.90–1.26)	1.08 (0.91–1.27)	1.07 (0.91–1.26)
2	198	91	452	1.04 (0.86–1.27)	1.02 (0.84–1.25)	1.02 (0.84–1.24)	1.00 (0.82–1.22)
3-4	155	70	358	1.05 (0.85–1.31)	1.04 (0.84–1.29)	1.04 (0.84–1.29)	1.04 (0.84–1.29)
5	247	106	572	1.01 (0.84–1.21)	0.98 (0.81–1.17)	0.99 (0.82–1.19)	0.97 (0.81–1.17)
Sauna use, times/month							
Never	2,849	1255	6487	Reference	Reference	Reference	Reference
1–2	141	55	336	0.87 (0.68–1.11)	0.84 (0.66–1.08)	0.86 (0.67–1.11)	0.87 (0.68–1.12)
ŝ	51	25	120	1.08 (0.76–1.53)	1.03 (0.72–1.46)	1.04 (0.73–1.48)	1.04 (0.73–1.48)
Hot tub/bath use, times/month							
Never	2,104	934	4782	Reference	Reference	Reference	Reference
1–2	714	317	1639	0.98 (0.87–1.10)	0.97 (0.87–1.09)	0.99 (0.88–1.11)	0.99 (0.88–1.11)
3	223	84	522	$0.84\ (0.68 - 1.03)$	$0.86\ (0.70{-}1.05)$	0.87 (0.70–1.07)	$0.86\ (0.70{-}1.06)$
Use of seat heaters, hours/week							
None	2,149	934	4897	Reference	Reference	Reference	Reference
0–2	535	249	1230	1.09(0.90-1.30)	1.01 (0.89–1.14)	1.01 (0.89–1.14)	1.02 (0.90–1.15)
3	355	151	811	0.82 (0.63–1.08)	0.97 (0.83–1.13)	0.97 (0.83–1.14)	0.97 (0.83–1.14)
Type of underwear worn							
Loose boxer/none	783	341	1812	Reference	Reference	Reference	Reference
Alternate loose/slim-fit briefs	333	135	775	0.93 (0.78–1.12)	0.94 (0.78–1.12)	0.94 (0.79–1.13)	0.94 (0.78–1.12)
Slim-fit briefs/boxer	1,921	857	4347	1.04 (0.93–1.17)	1.03 (0.92–1.16)	1.04 (0.93–1.16)	1.04 (0.92–1.16)
Time spent sitting, hours/day							
<5	711	324	1612	Reference	Reference	Reference	Reference
5-9	1,786	785	4099	0.96 (0.85–1.08)	$0.94\ (0.83 - 1.06)$	$0.94\ (0.83{-}1.06)$	0.93 (0.83–1.05)
10	544	226	1232	0.92 (0.79–1.07)	$0.94\ (0.80{-}1.10)$	$0.94\ (0.80 - 1.10)$	0.96 (0.82–1.13)
Fever episode in past 3 months							

Andrology. Author manuscript; available in PMC 2023 November 01.

Author Manuscript

Author Manuscript

Author Manuscript

Selected male heat exposures and fecundability, restricted to first 3 cycles of follow-up (2013-2021) Table 2.

<u> </u>
S
Õ
¥.
<u> </u>
0
t
-
D

Author Manuscript

Exposure	No. of Men	No. of Conceptions	No. of Cycles	Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b	Adjusted FR (95% CI) ^c
No	2,675	1178	8609	Reference	Reference	Reference	Reference
Yes	366	157	845	0.92 (0.77–1.10)	0.94 (0.79–1.12)	0.94 (0.79–1.12)	0.96 (0.81–1.14)
Truncated at 1 cycle of follow-up							
No	2,675	552	2675	Reference	Reference	Reference	Reference
Yes	366	60	366	$0.84\ (0.64{-}1.10)$	0.85 (0.65–1.11)	0.85 (0.65–1.11)	0.87 (0.67–1.14)
Cumulative heat metric ^d							
0 heat factors	642	285	1481	Reference	Reference		Reference
1 heat factor	1393	610	3,170	1.01 (0.89–1.15)	0.99 (0.87–1.12)		0.99 (0.87–1.12)
2 heat factors	758	347	1733	1.02 (0.88–1.18)	1.03 (0.89–1.19)		1.04 (0.90–1.20)
3 heat factors	194	74	437	0.92 (0.73–1.17)	0.94 (0.74–1.19)		0.95 (0.75–1.20)
4 heat factors	54	19	122	0.81 (0.53–1.24)	0.77 (0.50–1.17)		0.79 (0.52–1.20)
Cumulative heat metric ^e							
0 heat factors	646	285	1481	Reference	Reference		Reference
1 heat factor	1304	576	2987	1.02 (0.89–1.16)	0.99 (0.87–1.13)		0.99 (0.87–1.13)
2 heat factors	583	261	1305	1.04 (0.89–1.21)	1.04 (0.89–1.21)		1.04 (0.89–1.21)
3 heat factors	115	43	266	0.87 (0.64–1.17)	$0.86\ (0.64{-}1.16)$		0.87 (0.64–1.17)
4 heat factors	27	13	59	1.08 (0.65–1.80)	1.00 (0.60–1.68)		1.01 (0.60–1.69)
^a Adjusted for age, race/ethnicity, educ:	ation, total MET	Γs, alcohol intake, Bl	MI, cigarette smol	king, sleep duration, hours work	ed, unemployed, household	d income, and previously f	athered a child.

Andrology. Author manuscript; available in PMC 2023 November 01.

 b_b Mutually adjusted for other heat exposures when applicable, including sauna, bath, type of underwear, sitting, fever, laptop use on lap, and seat heater use.

 $\mathcal{C}_{\rm Further}$ adjusted for female age, intercourse frequency, and female BMI.

d'. Heat factor" defined as 3 saunas/month, 3 hot baths/month, tight fitting underwear, sitting 10 hours/day, fever, laptop use 5 hours/day, or seat heater use 3 hours/week.

^e.Heat factor" defined as in footnote d, but without fever. Analyses are also restricted to males without fever in the 3 months before enrollment.

-
_
–
_
-
\mathbf{O}
\sim
_
_
-
<
\leq
\leq
≤a
Mar
Man
Mani
Manu
Manu
Manus
Manus
Manusc
Manusc
Manuscr
Manuscri
Manuscri
Manuscrip
Manuscript

Author Manuscript

Table 3.

Cumulative heat metric and fecundability (restricted to first 3 cycles of follow-up), stratified by attempt time at enrollment, infertility history, and age

McKinnon et al.

	riegnancy au	empt time at enrollment				Male age a	t baseline	
		<3 cycles	No history of i	nfertilityat baseline	V	30 years		30 years
	Number of males	Adjusted FR (95% CI) ^a	Number of males	Adjusted FR (95% CI) ^a	Number of males	Adjusted FR (95% CI) ^a	Number of males	Adjusted FR (95% CI) ^a
Cumulative heat metric ^b	_							
0 heat factors	464	Reference	595	Reference	225	Reference	421	Reference
1 heat factor	960	1.03 (0.92–1.16)	1265	1.00 (0.87–1.13)	488	1.14(0.91 - 1.42)	896	0.90 (0.77–1.05)
2 heat factors	544	1.03 (0.90–1.18)	700	1.02(0.88 - 1.18)	273	1.35 (1.05–1.74)	496	0.89 (0.74–1.07)
3 heat factors	129	1.01 (0.82–1.24)	172	0.96 (0.75–1.22)	60	1.09 (0.72–1.65)	130	$0.85\ (0.64{-}1.14)$
4 heat factors	44	0.75 (0.51–1.11)	50	0.73(0.48 - 1.13)	18	1.17 (0.62–2.22)	34	0.60(0.34 - 1.04)
Cumulative heat metric $^{\mathcal{C}}$								
0 heat factors	464	Reference	595	Reference	225	Reference	421	Reference
1 heat factor	897	1.00 (0.86–1.16)	1194	1.00(0.87 - 1.14)	450	1.16 (0.92–1.45)	854	$0.90\ (0.77 - 1.05)$
2 heat factors	424	1.05 (0.89–1.25)	535	1.01(0.86 - 1.18)	205	1.35 (1.04–1.76)	378	0.90(0.74 - 1.09)
3 heat factors	74	0.98 (0.71–1.36)	106	0.87 (0.65–1.18)	33	0.86 (0.50–1.50)	82	$0.84\ (0.59{-}1.19)$
4 heat factors	21	1.09 (0.65–1.86)	26	0.95 (0.56–1.62)	6	1.42 (0.68–2.95)	18	0.76 (0.38–1.52)
^a Adjusted for age, race/ett	micity, education,	total METs, alcohol intake, B	MI, cigarette smok	ing, sleep duration, hours v	vorked, unemploy	yed, household income, pr	eviously fathered	a child.
b"Heat factor" defined as	3 saunas/month,	3 hot baths/month, tight fitti	ng underwear, sittir	ig 10 hours/day, fever, lar	top use 5 hours/	/day, or seat heater use 3	hours/week.	

Andrology. Author manuscript; available in PMC 2023 November 01.

^c.Heat factor" defined as in footnote d, but without fever. Analyses are also restricted to males without fever in the 3 months before enrollment.