



Hypertension and semen quality among 1381 young men: A cohort study with repeated measurements

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Dear Editor,

Hypertension, defined as persistent diastolic blood pressure (BP) of at least 80 mmHg or systolic BP of at least 130 mmHg,¹ affects over 1 billion adults worldwide. Hypertension is not only a well-known risk factor for cardiovascular diseases and mortality, but also has been associated with reduced human fertility. Semen quality is the most important indicator of male fertility. Toxicological studies have demonstrated that hypertension adversely affects sperm concentration, morphology, acrosomes, DNA integrity, and mitochondrial activity in different animal models (e.g., mice and rats).² Several population studies also have explored the association between hypertension and semen quality in men, but the results are divergent.³⁻⁷ Major weaknesses of previous studies included their cross-sectional study design, a lack of adjustment for various demographic characteristics and lifestyle factors (e.g., body mass index, alcohol consumption, and physical activity), and a single measurement of semen quality per participant. More importantly, these previous studies mostly recruited men from an infertility clinic or male partners of infertile couples. To date, no study has examined the association between hypertension and semen quality among young men from the general population, nor explored effect modification by lifestyle factors, which are important for improving preventive interventions. Therefore, we a) examined the association between hypertension and semen quality among 1381 young men screened as potential sperm donors who provided 6441 repeated semen samples over an approximately 3-month period, and b) examined the potential effect modification by lifestyle factors.

DATA SOURCES FOR THIS STUDY

From April 2017 to July 2018, we recruited 1487 young men (22-45 years) screened as sperm donors, irrespective of whether their semen quality met the donation standards, from the Hubei Province Human Sperm Bank in China.¹ At recruitment, participants completed a structured questionnaire and underwent a physical and semen examination. Given the considerable within-person variability of sperm quality parameters,⁸ semen samples were repeatedly collected from each participant during a 3-month follow-up period, which corresponds to the duration of spermatogenesis.⁹ After excluding 102 men with physician-diagnosed medical conditions that may affect reproductive health, 2 without BP measurements, and 2 diagnosed with azoospermia, 1381 men were included in the present study.

ASSESSMENT OF SEMEN QUALITY AND HYPERTENSION

BP was measured at a single time point at recruitment, given that existing literature recommends monitoring hypertension every 1-3 years in healthy adults without antihypertensive treatment. BP was measured at recruitment according to the guidelines of the Chinese and American Heart Association.¹ We calculated pulse pressure (systolic BP - diastolic BP) and arterial pressure [$1/3 \times (\text{systolic BP}) + 2/3 \times (\text{diastolic BP})$]. Stage 1 hypertension was defined as systolic BP of 130-139 mmHg or diastolic BP of 80-89 mmHg, and stage 2 hypertension as systolic BP of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg.¹ Semen samples were collected in a private room through masturbation both

at baseline and during the 3-month follow-up period.⁸ Sperm quality parameters were measured by professional technicians according to the World Health Organization (WHO) laboratory manual.⁸

STATISTICAL ANALYSIS

Descriptive analyses were conducted for participants' characteristics, BP measurements, and sperm quality parameters. Multivariable linear mixed regression models were used to estimate regression coefficients of repeated sperm quality parameters according to hypertension (i.e., stage 1 and stage 2 hypertension). Due to the skewed distribution of sperm quality parameters, ln-transformed values were used in multivariable regression models. The obtained regression coefficients were then back-transformed to derive percentage changes using the formula $[(\exp(\beta) - 1) \times 100\%]$.¹ Generalized additive mixed models were used to evaluate the linearity and associations between continuous measurements of BP and sperm quality parameters using the effective degrees of freedom (EDF) method.

Potential confounders were selected based on prior knowledge, including age, BMI, educational background, marital status, household income, smoking status, alcohol consumption, sampling season, abstinence day, sleep quality, and moderate-to-vigorous activity. To assess effect modification by lifestyle factors, stratified analyses were conducted according to BMI, smoking status, alcohol consumption, moderate-to-vigorous physical activity, and sleep quality, using the cutoffs identified in previous studies.⁸ The interaction was evaluated using the Chi-sq test.

DESCRIPTIVE ANALYSES

Among the 1381 young men [median age (25th, 75th): 27 (24, 31) years] included in the present analysis, 361 (26.1%) and 124 men (9.0%) were diagnosed with stage 1 and stage 2 hypertension, respectively (Figure 1A). A total of 6441 semen samples were collected from 1381 men at baseline and during the 3-month follow-up [mean $\pm$ SD: 4.7 $\pm$ 4.3 times per participant]. The corresponding mean (SD) semen volume, sperm concentration, total count, total motility, and progressive motility were 3.1 (1.4) mL, 56.1 (23.6) million/mL, 169.1 (94.5) million/ejaculation, 60.1 (11.9) %, and 56.9 (12.1) %, respectively. The morphology of sperm was measured for 2022 semen samples from 1355 men (Figure 1A).

MAIN ANALYSES

In adjusted models, men with stage 1-2 hypertension exhibited a lower sperm morphology, progressive motility, and total motility of -6.12% (95% CI -13.11%, 1.43%), -2.55% (95% CI -5.05%, 0.02%), and -2.65% (95% CI -4.92%, -0.33%), respectively, as compared to men without hypertension (Figure 1B). When we classified participants into three groups (i.e., no hypertension, stage 1 hypertension, and stage 2 hypertension), there were clear dose-response relationships across the severity of hypertension (all P for trend < 0.06; Figure 1B). When BP parameters were treated as continuous variables, we observed inverse associations between diastolic BP and progressive and total sperm motility, and between mean arterial pressure and progressive and total sperm motility. For sperm quality parameters associated with stage 1-2 hyperten-

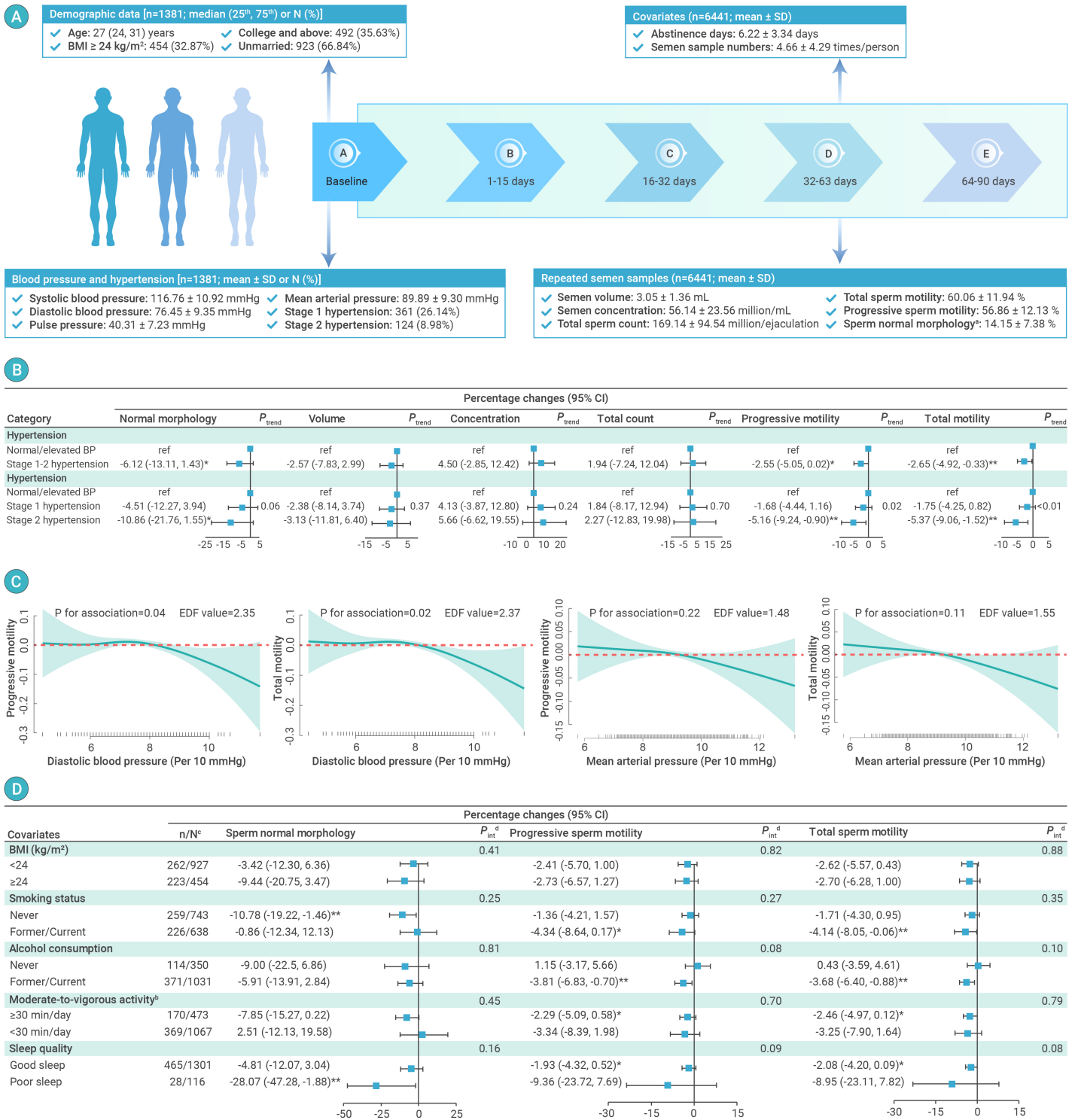


Figure 1. (A) Demographic characteristics, distribution of blood pressure, and repeated semen quality parameters of study participants (N=1381). (B) Percentage changes (%) in semen quality parameters in relation to hypertension among study participants based on linear mixed models. Sperm quality parameters were ln-transformed. Models were adjusted for age, BMI, education levels, marital status, household income, smoking status, alcohol consumption, sampling seasons, abstinence time, sleep quality, and moderate-to-vigorous activity. (C) Dose-response relationships between blood pressure (per 10 mm Hg) and semen quality parameters based on generalized additive mixed models, with the adjustment for the same set of covariates in Figure 1B. Sperm quality parameters were ln-transformed. (D) Stratification and interaction analyses for percentage changes (95% CI) in repeated semen quality parameters in relation to hypertension, with the adjustment for the same set of covariates in Figure 1B. ^aIn total, 2022 semen samples were analyzed for morphology. ^bPhysical activity refers to moderate-to-vigorous activity. ^cn and N represent the number of men with stage 1-2 hypertension and no hypertension, respectively, in each stratum. ^dP for interaction. * $P < 0.15$; ** $P < 0.05$. Abbreviations: SD, standard deviation.

sion, we further used generalized additive mixed models to evaluate the linearity and associations between continuous measurements of BP and these sperm parameters. We found inverse non-linear associations between diastolic BP and progressive motility and total motility ($EDF = 2.35$ and 2.37 , respectively), with the declining trend becoming steeper as diastolic BP

increased (Figure 1C). Mean arterial pressure was inversely associated with progressive motility and total motility in a monotonic linear manner ($EDF = 1.48$ and 1.55 , respectively; Figure 1C). All individual BP measurements were unrelated to sperm morphology (data not shown). Stratified analyses showed that the inverse associations of hypertension with progressive and total

sperm motility were stronger among men who drank alcohol (P for interaction = 0.08 and 0.10, respectively) and those who had poor sleep quality (P for interaction = 0.09 and 0.08, respectively; Figure 1D).

Animal experiments in rats have demonstrated that systemic arterial hypertension induced testicular vascular alterations, impaired sperm DNA integrity, and led to dysfunctional mitochondria and intracellular superoxide anion activity.² A recent study reported that hypertension adversely affected hormone receptors, the expression of steroidogenic enzymes, and secretory proteins in the testes of mice, which were in line with damaged sperm acrosome, nonfunctional mitochondrial activity, and increased abnormal morphology. Several human studies also have explored the associations between hypertension and semen quality,³⁻⁷ but the results are divergent. Our findings were consistent with a previous cross-sectional study, showing that hypertension was associated with a greater risk of abnormal sperm morphology among 8395 men attending a private medical screening program in Taiwan.⁴ In a US study, Eisenberg and colleagues reported higher rates of semen abnormalities (i.e., volume, motility, and total count) among 9387 men from a US infertility clinic with versus without hypertensive disease.⁵ In a more refined study consisting of >1000 men from infertile couples, Guo and colleagues reported that hypertensive men exhibited lower sperm motility than men without hypertension.⁶ However, they also reported a lower semen volume and sperm concentration, which were not observed in our present study.⁶ A recent Chinese retrospective cohort study reported that hypertension was associated with reduced sperm quality parameters (e.g., total sperm motility, total count, progressive motility, and progressive count), as well as lower clinical pregnancy and live birth rates among male partners of 1043 couples from a reproductive medicine center.⁷ However, a lack of association between hypertension and semen quality has also been reported.³

The divergent results between studies could be partly driven by the differences in population composition (e.g., infertile vs. healthy men), study design, and the number of semen quality measurements per participant. In our present study population, we found considerable within-person variability in repeated measurements of semen volume, sperm motility, concentration, and total count over 3 months (intraclass correlation coefficient: 0.2-0.6).⁸ Our present study refines and strengthens previous evidence. We used repeated measurements of sperm quality parameters over a 3-month follow-up period (mean: 4.7 ± 4.3 times per participant) and collected detailed data on confounding and lifestyle factors. We found that the association of hypertension with sperm motility was stronger among men with several adverse lifestyle factors, particularly poor sleep quality and alcohol intake. The observed interaction is not unexpected given the well-documented evidence of associations between alcohol consumption and poor sleep quality and reduced semen quality. For instance, poor sleep quality has been associated with perturbations in the circadian rhythm, increased apoptosis in seminiferous tubules, and down-regulated marker genes of post-spermatocyte stage cells, potentially leading to reduced semen quality.⁸ However, it should be noted that the inverse associations between hypertension and progressive and total sperm motility persisted among men with good sleep and no alcohol intake, suggesting that hypertension itself is a potential risk factor for reduced semen quality. Additionally, we separately assessed the associations for semen quality in relation to stage 1 and 2 hypertension, finding clear dose-response relationships across the severity of hypertension, yet only men with stage 2 hypertension had significantly lower semen parameters compared to normotensive men. In support of this notion, generalized additive mixed models demonstrated non-linear inverse associations between diastolic BP and progressive motility and total motility, with the declining trend becoming steeper as diastolic BP increased.

The strengths of our present study include its prospective study design, large population size, repeated measurement of semen quality at multiple time points per participant, and extensive collection of various confounding and lifestyle factors. Additionally, we recruited young healthy men screened as potential sperm donors, which may be more representative than the previous studies that only included subfertile men and men from hospitals.³⁻⁷ However, our study has some limitations. First, we measured BP at a single time point at recruitment and therefore may have misclassified the true BP of some men, given the considerable variability of BP over time. However, previous studies have suggested monitoring hypertension every 1-3 years in healthy adults without antihypertensive treatment.¹ Second, although we have adjusted for extensive confounding and lifestyle factors, confounding from unmeasured factors cannot be fully ruled out. Third, causal relationships should be interpreted with caution.

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PERSPECTIVE AND CLINICAL IMPLICATIONS

In China, the prevalence of hypertension is nearly 50% among a nationally representative sample of 451,755 adults from 31 provinces.¹⁰ Hypertension is not only a well-known risk factor for cardiovascular diseases and mortality, but also has been associated with reduced human semen fertility.³⁻⁷ In the present study consisting of 1381 healthy young men with 6441 repeated measurements of semen quality over 3 months, we found that hypertension, especially stage 2 hypertension, was associated with reduced sperm morphology, progressive motility, and total motility. We also found evidence of interaction between hypertension and modifiable certain lifestyle factors, including sleep and alcohol intake. Our findings underscore the importance of preventing hypertension in improving male fertility and point to potential lifestyle interventions to mitigate semen quality decline in hypertensive men.

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AUTHOR CONTRIBUTIONS

GL analyzed the data. GL and YW drafted the manuscript. CL and LJ validated the accuracy of the data analysis. CL, LJ, and YW directed the analysis and made major comments/edits to the manuscript. All authors contributed to the interpretation of results and critically reviewed the manuscript for important intellectual content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

The study has been approved by the Ethics Committee of the Reproductive Medicine Center, Tongji Medical College (approval No. [2017] IEC [No.1]).

DATA AND CODE AVAILABILITY

Not applicable.

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