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Male exposure to bisphenol A (BPA) and semen quality in the Home Observation of Periconceptional Exposures (HOPE) cohort

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Abstract

Background: Exposure to bis-phenol A (BPA) has been associated with reduced semen quality. The objective of this study was to examine associations between BPA measured in serial daily first-morning urine samples and semen quality parameters among men trying to conceive.

Methods: This prospective, preconception cohort included 161 men ages 18–40 without known subfertility. Men collected daily, first morning urine during their female partner's fertile window. Semen samples were collected through intercourse after the fertile window.

Results: Samples from 161 men were analyzed. Higher geometric mean (GM) BPA exposures (ng/mL) were found among men with abnormal sperm tail morphology (GM=3.12, 95% CI=2.43, 4.01) compared to men with normal morphologic findings (GM=2.39, 95% CI=2.17, 2.74). There was no association with sperm count.

Conclusion: Higher exposure to BPA was associated with abnormal sperm tail morphology in this prospective, pre-conception cohort.

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Conflicts of interest:
The authors have no conflicts of interest to declare

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available upon request.

Keywords

Semen quality; BPA; preconception cohort

Introduction

Both versatile and common, the industrial chemical bisphenol A (BPA) is produced at a rate of five to six million pounds annually [1, 2]. It is used in many consumer products, including the lining of water supply pipes, aluminum cans, reusable plastic food containers, dental sealants, thermal receipts, medical equipment, and building supplies [1–3]. Its widespread use translates into myriad opportunities for human exposure; BPA can leach into food or liquid in the presence of either acidity or alkalinity,[2] or during normal use of commonly used products such as polycarbonate containers [3]. Additionally, dermal absorption may occur, especially when handling thermal receipt paper, as may inhalation exposure in the form of dust [1, 4, 5]. Given the breadth of exposure, it is unsurprising that the vast majority of the world's population has some amount of BPA detectable in their urine at any given time[6]; in the United States, more than 90% of participants in the 2011–2012 National Health and Nutrition Examination Survey had BPA levels above the limit of detection (0.4 μg/L) [1]. Concern has grown in recent decades about the impact of this level of exposure.

In animal models, BPA has been shown to disrupt hormone-signaling systems in a variety of ways,[7, 8] including interactions with receptors as an agonist or antagonist by binding to receptors, and actions that impact hormone synthesis and clearance [8]. This has been observed at a wide range of doses in animal models [8, 9]. When exposed to levels of BPA below the current lowest observed adverse effect level of <50 mg/kg, adult male rodents show decreased serum testosterone levels and diminished sperm quantity, motility, morphology, and increased sperm DNA damage [10–13].

In human epidemiological studies negative associations have been reported between BPA levels and semen concentration,[14–18] sperm count,[14, 16–18] vitality,[14, 16] motility, [14, 15, 19] morphology,[15, 17] and increased DNA damage [15]. However one study observed reduced sperm DNA damage with increased BPA,[20] another showed a positive relationship between higher BPA levels and higher testosterone levels [21]. Several studies found no associations between BPA and seminal quality [22–24]. However, it is difficult to draw generalized conclusions from these studies: several took place at fertility clinics or among men known to be sub-fertile,[15–17, 23, 24] while others recruited men known to be fertile,[22] from the general population,[18, 20, 21] or from occupations with known BPA exposure [14]. Additionally, exposure ascertainment varied; while most studies used urine samples, Vitku, et al., collected seminal and plasma BPA [17].

A major consideration when interpreting this literature is the cross-sectional nature of the exposure and outcome ascertainment; most referenced studies used a single urine sample to measure BPA, the one exception used 24 hour urine collection [21]. Multiple studies have found large between-day variability in BPA measurements, leading to calls for repeated sampling as a more reliable indicator of exposure level [25–29]. Given the dynamism of the spermatogenesis cycle, which may be significantly more vulnerable to exogenous factors

during some phases,[30–32] as well as the transient nature of BPA exposure, this model may lead to exposure misclassification [33]. For non-persistent chemical exposure ascertainment, urine has been shown to contain concentrations of metabolites 30–100 times higher than those found in plasma and other lipid-rich biological fluids, allowing more precise and reliable quantification, as long as the urine samples span a sufficient time frame to account for variability of exposure [34, 35].

The present study seeks to examine the relationship between BPA level and parameters of sperm quality, using multiple urine samples for each participant. Exposure was measured through repeated daily, home-based urine testing during partners' fertile windows. Outcome was measured by semen collection.

Methods

Study population

As part of the Home Observation of Periconceptional Exposures (HOPE) study, the study population consisted of 183 heterosexual couples seeking to become pregnant within three months of enrollment. Participants were recruited from the Salt Lake City, Utah area beginning in January of 2012 and had no known fertility issues. Female participants were required to be between 18 and 35 years old, and males were required to be between 18 and 40. Recruitment and study design is more fully detailed elsewhere [36]. This study was approved by the University of Utah Institution Review Board (IRB).

Urine sample collection

At enrollment, female participants were instructed in a previously validated method of observing changes in cervical mucus to estimate day of ovulation (EDO) and fertile window [37]. These observations – as well as other relevant information relating to potential lifestyle exposures to alcohol, cigarette smoke, illness, and stress – were recorded on a fertility chart. Male partners collected daily, first-morning urine beginning the first day fertile-quality mucus was observed by the female partner. They continued collection until two days after the EDO, a collection window of approximately seven days each menstrual cycle. If pregnancy was not achieved during the first cycle, couples completed a second. In cases where first-morning urine was not collected, participants were asked to collect as soon as they remembered and mark the specimen indicating when it was collected. Urine was collected in 4-oz polypropylene specimen cups and then transferred into 50-mL polypropylene tubes and frozen in participants' home freezers. The specimen collection containers were selected to not contain BPA, per the manufacturer's specifications and verified by lab quality control procedures. At the end of each cycle, study staff members collected participant samples, which were taken to the Center for Human Toxicology at the University of Utah for analysis.

BPA Analysis

Urine samples were stored at −20°C at the laboratory before and after processing. Ultra-high-performance liquid chromatography-tandem mass spectrometry was used to measure total BPA as unconjugated BPA plus mono-glucuronide conjugate and mono-sulfate

conjugate, using chemistry methods and quality control procedures previously described in detail[38]. This method used liquid/liquid extraction with 1-chlorobutane and a human urine aliquot sample of 800 μL. Chromatography was performed using an Acquity UPLC® system (Waters Corporation, Milford, MA) with a Kinetex® Phenyl-Hexyl column (Phenomenex, Torrance, CA). Mass Spectrometric analysis was performed using negative electrospray ionization on a Quattro Premier XE™ (Waters Corporation). The acceptance criteria applied for analytic standards and quality controls was ± 20% of nominal concentration, the limit of detection was .1 ng/mL and the limit of quantification was .75 ng/mL as is standard procedure by WHO guidelines. A total of 186 samples (13.0%) were below the limit of quantification and were assigned a value of LOQ divided by the square root of 2, or 0.53 ng/mL [39]. Laboratory glassware, consumables, reagent chemicals, and all consumables throughout the chain of custody were verified as BPA-free by laboratory assay prior to use. We have previously published a more technical reporting of the method development including the quality control procedures and coefficients of variation (within acceptable limits) [38].

Semen Collection

Semen was collected at least 3 days after the EDO and before the start of the next menses at EDO+ 18 days, after the close of female partners' fertile window as estimated by cervical mucus observation. This window of collection ensured that semen collection did not interfere with the probability of conception. Semen samples were collected via intercourse, or in some cases masturbation, using a Male-FactorPak™ semen collection device (Apex Medical Technologies, San Diego, CA), which is a specially made condom that can be sealed after semen collection. They were frozen in the participants' home freezers until the end of each cycle, when they were collected by study staff. A maximum of two semen samples were collected by each male participant during the study.

Semen Analysis

Semen analysis was carried out at the Division of Andrology at the University of Utah. Samples were kept at −20°C until analysis, after which remaining sample was refrozen. Samples were assessed for total volume, sperm concentration, sperm count, and morphology characteristics according to the World Health Organization criteria [40]. To defrost, samples were placed on a 37°C warming plate for 20–30 minutes. Sperm count was conducted using a Makler chamber, into which a drop of semen sample was loaded; it was then heated on a 50°C hot plate for at least 2 minutes, then allowed to cool. A microscope with a 20x objective lens was used and sperm heads in one row of squares were counted, giving a count in millions per mL. Concentration was calculated by multiplying the sperm count by the semen sample volume in mL. Morphological examination was performed using a Brightfield microscope; x1000 magnification was used, with oil immersion. Well-mixed semen was thinly spread on clean slides, then allowed to air dry, followed by staining by immersion into subsequent baths of methanol, water, hematoxylin, water, ammonia water, water, eosin, and increasing strengths of alcohol, then Americlear. Slides were covered and allowed to dry for 1–2 hours before examination. A minimum of 100 sperm cells were counted from each specimen and assessed for head shape (amorphous, tapered, bicephalic, megalohead,

microhead, immature head), neck and midpiece abnormalities, and tail abnormalities (micro tail, bent tail, coiled tail, lack of tail).

Statistical Analysis

For each participant, we calculated the geometric mean (GM) BPA level across all samples for each cycle; the geometric mean was used due to the non-normal distribution of the data. We performed this calculation with and without adjustment for creatinine and specific gravity, and found neither correction altered the BPA concentrations appreciably (mean 19% relative change).As there were no meaningful differences between the adjusted and adjusted BPA, unadjusted GM BPA was used in subsequent calculations. The resulting GMs were classified into low, medium, or high tertiles of exposure for that cycle.

Semen and sperm parameters were converted to dichotomous variables, using 5th edition WHO guidelines for abnormality cut-off levels [40]. The following were used for thresholds as abnormal: concentration <15 million/mL; volume <1.5 mL; total sperm count <60 million/ejaculate; morphology with <30% of an examined sample containing normal heads; <65% containing normal tails; >5% of the heads in a sample being classified as either megaloheads or microheads; >35% tapered heads; >5% bicephalic heads; >10% amorphous. We also evaluated the semen and sperm parameters as continuous predictors and the results were not significantly different from the dichotomized outcomes.

Mean GM BPA levels were calculated for normal and abnormal levels of each semen parameter; these were tested for difference using a Mann Whitney test. Generalized estimating equation (GEE) models with a log-link and repeated measures for each cycle were used. The GM BPA of each cycle was used and a binomial distribution was used to account for the dichotomous outcome variables in each model. Models were run with GM BPA as a continuous variable and in tertiles. Models were adjusted for potential confounders identified a priori, including body mass index (BMI), race, income, smoking, and age[38, 41–45]. Smoking was found to be collinear with a combination other variables, including age, BMI, and race, in several models and was therefore removed from those models. Smoking status — current, former, or never smoker — was self-reported. The false discovery rate was utilized to account for multiple comparison, which gives a multiple comparison corrected p-value.

Results

161 men were included in this analysis. They contributed a total of 1431 urine samples (mean 8.9 per person; all used in the analysis) and 244 semen samples (83 men had two samples). The mean participant age was 28.5 (SD 3.9); the majority of participants were white (88.8%) and had completed at least four years of college (57.1%). Income was normally distributed, with 36% of participants earning between 40 and 75 thousand dollars per year and most being employed (64.6%), though a large minority were students (29.2%). The mean BMI was 27.1 (SD 5.9) and most participants (88.2%) had never smoked (Table 1). The only parameter showing significantly different BPA GMs in men with normal and abnormal levels of included semen parameters was total percentage of normal tails (p=0.0324), as shown in Table 2.

In the regression models with GM BPA as a continuous variable, only a proportion of normal heads <30% was significantly associated with BPA (PR=1.14, 95%CI=1.02, 1.28)), as shown in Table 3. However adjusting for multiple comparisons, this finding was no longer significant. There were no significant associations of tertiles of BPA exposures with semen parameters, and only one of the parameters (<65% tails) would be suggestive of a dose-response pattern (Table 4).

Discussion

This study adds to the expanding field of literature examining the relationship between environmental factors and male reproductive health. It also demonstrated the utility of a home-collection methodology for both urine and semen.

Previous studies have shown a mix of positive, negative, and null associations between BPA and semen quality parameters. These findings include the association of higher BPA concentration and decreased sperm count and concentration, and with higher levels of abnormal morphology and DNA damage [15]. Vitku, et al. reported plasma BPA levels negatively correlated with sperm motility, and semen BPA was negatively correlated with normal morphology, as well as with total sperm count and concentration [17]. However, several other studies have observed inverse relationships with BPA concentration and sperm count, vitality, concentration and motility [14, 16].

We did not observe any association between BPA and semen parameters such as tail morphology or sperm concentration. Further, because of our design, we were unable to assess motility. However, several other studies have reported contrary or null findings. A study of men from the general population by Lassen, et al., also found an association between higher BPA concentration in urine and low sperm progressive motility; no other associations were found with semen parameters [19]. A case-control study with men recruited from fertility clinics found no associations between BPA and semen parameters, though a negative correlation was found with testosterone level [23]. A more recent study of young men from the general population by Adoamnei and associates found inverse associations between urinary BPA and sperm count and concentration, but no association with morphology [18]. In a study led by Goldstone, the only significant finding was of a negative relationship between BPA concentration in urine and DNA fragmentation [20]. Chen and associates conducted a case-control study with men having idiopathic infertility; they found no relationships between BPA and semen parameters. A study of the partners of pregnant women also found no significant associations between BPA concentration in urine and semen parameters [22].

There are several limitations to the previous studies that make generalizability and comparability difficult. First, these studies all use different populations of men with different exposures and outcomes. This is especially true of studies utilizing men of known or suspected subfertility, whose irregular semen parameters may or may not relate to BPA [15–17, 23, 24]. An additional difficulty for comparing previous studies is the wide range of GM BPA ranging from 0.55 ng/mL[20] to 3.59 ng/mL [19, 21]. Our study falls in the middle of this range with a GM BPA of 2.50 ng/mL.

As a transient exposure, BPA levels can have wide intra-subject variability [25, 26]. Because nearly all reviewed studies relied on one sample for exposure ascertainment, interpreting associations with semen parameters (which develop over the course of the spermatogenesis process) is difficult[15, 16, 18–22]. This emphasizes the importance of collecting multiple samples over well-defined period of time. Previous work published by our group found that the interclass correlation coefficient for repeated daily BPA samples was only .18 for the males in our study; when BPA concentrations were divided into tertiles, five samples were required to reach sensitivity and positive predictive values ≥ .75 for the high and low tertiles; the medium tertile was less accurate even with five samples [25]. Other researchers have had similar results [26, 27]. Therefore, a strength of our study is that we had a mean of 8.9 daily samples per participant. However, although the exposure assessment for BPA occurred prior to the outcome assessment of semen quality, it was not aligned with the early stages of spermatogenesis, which begins about 2 months prior to the ejaculation of the sperm[46, 47].

Other strengths of our study include high compliance among participants. We believe that this enabled us to build a more accurate picture of individuals' BPA exposure over time. This is belief is strengthened by the moderate correlation observed between BPA concentrations at cycle 1 and cycle 2 (Spearman correlation p= 0.64, p<.0001) and more fully described elsewhere [25]. Our compliance among male participants for urine collection ranged between 56–75%; semen collection compliance was 90% [36]. Use of home-based collection methods and semen collection via a seminal collection device that can be used with intercourse may have supported compliance; future researchers may wish to consider this collection paradigm as an alternative to masturbation samples, which may be less acceptable to some couples. Our overall compliance included a high retention; in spite of an intensive sample-collection schedule, our dropout rate was 6% [36].

Limitations of our study include a comparatively racially and socio-economically homogenous study population; these characteristics may impact BPA levels and limit generalizability of results to other populations. The very low smoking rates observed in our population, however, allowed for less confounding in our analysis. A draw-back of the home-based collection methodology was that semen was frozen, and thus could not be used for tests of motility. Difficulty was also encountered by some participants in handling the samples, resulting in unreliable volume measurements; some participants also reported discomfort encountered with the FactorPak™ condom used for semen collection. Future study protocols could anticipate this issue and provide more instruction or alternate collection and storage solutions. Also, as semen could have been collected through either intercourse with the FactorPak™ or through masturbation, there is a slight chance that this could be a potential confounder. However, the majority were collected with the FactorPak™ and that should not have impacted the semen quality, particularly the morphologic parameters. Finally, we did not ask about time since last ejaculation 13 at the time of semen collection and therefore did not adjust for days since intercourse in our analysis; while this may have impacted some semen parameters; however, any effect would not be expected to be differential between those with higher and lower BPA concentrations. Further, while time of abstinence may affect semen volume and sperm concentration, it is not known to impact morphology parameters [48].

Future researchers may wish to include the newer bisphenols being used as replacements for BPA in their investigations; early research in animal models has shown impacts on male reproductive health and oocyte development at least as harmful as BPA, particularly in the case of bisphenols [4, 49]. New entrants on the chemical marketplace should be considered not just singly but as part of the comprehensive EDC exposure to which individuals are subjected in the course of their daily activities [4, 50].

In conclusion, this study did not demonstrate an association between higher BPA concentration and abnormal sperm morphology or concentration. Nevertheless, the study demonstrates the feasibility of field methods for higher accuracy of exposure assessment and the assessment of semen quality. This study shows the feasibility of in-home collection and storage of both semen and urine in the context of an observational, cohort study. Future studies should include multiple per-person urine samples, investigate a broader range of phenols and EDC exposures in diverse study populations, and respect participants' preferences regarding sample collection.

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Highlights

- Bis-phenol A (BPA) has been previously associated with reduced semen quality
- Increased exposure to BPA was associated with abnormal sperm tail morphology
- BPA was not associated with sperm count, volume, or concentration

Table 1:

Participant Demographic Characteristics

	n=161 mean ± SD or n (%)
Age (years)	28.5 ± 3.9
<25	20 (12.4)
25–35	132 (82.0)
>35	9 (5.6)
Race	
Caucasian	143 (88.8)
Other/Multiracial[a]	18 (11.2)
Hispanic	
Yes	12 (7.4)
No	148 (91.9)
Missing	1 (.6)
Education	
High School	8 (5.0)
College (1–3 years)	60 (37.3)
College (>4 years)	92 (57.1)
Missing	1 (.6)
Annual Income[b]	
<$20,000	21 (13.0)
$20,000-$39,000	46 (28.6)
$40,000-$74,999	58 (36.0)
$75,000-$99,000	20 (12.4)
≥$100,000	12 (7.4)
Missing	4 (2.5)
BMI[c]	27.1 ± 5.9
< 18.5	2 (1.2)
18.5–24.9	65 (40.4)
25.0–29.9	54 (33.5)
≥ 30	39 (24.2)
Missing	1 (0.6)
Smoking	
Current Smoker	5 (3.1)
Former Smoker	14 (8.7)
Never Smoker	142 (88.2)
Employment	
Employed for wages	104 (64.6)
Self-employed	4 (2.5)
Homemaker	1 (.6)
Student	47 (29.2)

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	n=161 mean ± SD or n (%)
Unemployed/Other[d]	4 (2.5)
Missing	1 (.6)

Abbreviations: SD (standard deviation), BMI (body mass index)

[a] Includes Asian, Black/African American, Pacific Islander, American Indian/Alaskan Native

[b] US Dollars, combined household income for both partners

[c] Body Mass Index: weight (kg)/height (m)^2 (measured at enrollment)

[d] Includes out of work, retired, unable to work

Table 2:

Urinary BPA Concentration in relation to Semen Parameters

	Men with normal semen parameter		Men with abnormal semen parameter		
Sperm Parameter	**n (%)**	**GM BPA (95% CI)**	**n (%)**	**GM BPA (95% CI)**	**p-value***
<30% normal heads	124 (50.8)	2.28 (2.03, 2.56)	120 (49.2)	2.75 (2.39, 3.17)	0.0567
<65% normal tails	199 (81.9)	2.39 (2.17, 2.63)	44 (18.1)	3.12 (2.43, 4.01)	0.0324
Concentration <15 million/mL	210 (86.1)	2.50 (2.27, 2.74)	34 (13.9)	2.54 (1.85, 3.49)	0.6896
Volume <1.5 mL	173 (70.9)	2.58 (2.33, 2.87)	71 (29.1)	2.31 (1.93, 2.77)	0.0878
Count <60 million	166 (68.0)	2.50 (2.24, 2.78)	78 (32.0)	2.51 (2.12, 2.98)	0.7936
>5% megaloheads	240 (98.4)	2.52 (2.30, 2.76)	4 (1.6)	1.76 (0.74, 4.19)	0.2888
>5% Microheads	233 (95.5)	2.51 (2.29, 3.76)	11 (4.5)	2.31 (1.62, 3.28)	0.7830
>35% tapered heads	159 (65.2)	2.48 (2.23, 2.77)	85 (34.8)	2.54 (2.15, 3.00)	0.7767
>5% bicephalic	240 (98.4)	2.49 (2.28, 3.73)	4 (1.6)	3.00 (0.41, 1.70)	0.6246
>10% amorphous heads	33 (13.5)	2.41 (1.81, 3.21)	211 (86.5)	2.52 (2.29, 2.77)	0.9979

*Mann Whitney test between geometric means of BPA

GM: geometric mean

Table 3:

Adjusted odds ratios for abnormal semen parameters by BPA levels (both cycles) with continuous GM BPA

Semen Parameter	Adjusted PR (95% CI)	p-value	FDR p-value
<30% normal heads[a]	1.14 (1.02, 1.28)	0.0224	0.3136
<65% normal tails[a]	1.13 (0.99, 1.28)	0.0081	0.2268
Concentration <15 million/mL[a]	1.07 (0.96, 1.20)	0.2169	0.6073
Volume <1.5 mL[a]	0.98 (0.87, 1.10)	0.9461	0.9811
Count <60 million[a]	1.01 (0.92, 1.12)	0.5841	0.8659
>5% megaloheads[b]	0.74 (0.50, 1.09)	0.1343	0.5372
>5% Microheads[a]	0.88 (0.72, 1.07)	0.2573	0.6549
>35% tapered heads[a]	1.03 (0.94, 1.12)	0.5807	0.8659
>5% bicephalic[b]	1.02 (0.83, 1.26)	0.8164	0.9416
>10% amorphous heads[c]	1.02 (0.90, 1.16)	0.9005	0.9698

[a]adjusted for age, race, income, smoking status, and body mass index (BMI)

[b]adjusted for age, income, and BMI (race and smoking status removed due to collinearity)

[c]adjusted for age, race, income, and BMI (smoking status removed due to collinearity)

GM: geometric mean, PR: prevalence ratio, FDR: False Discovery Rate

Table 4:

Adjusted odds ratios for abnormal semen parameters by BPA levels (both cycles) with GM BPA tertiles

	GM BPA tertiles						
	<1.81 ng/mL	**1.81–3.27 ng/mL**			**>3.27 ng/mL**		
Semen Parameter		**Adjusted PR (95% CI)**	**p- value**	**FDR p-value**	**Adjusted PR (95% CI)**	**p- value**	**FDR p-value**
<30% normal heads[a]	Reference	0.99 (0.51, 1.93)	0.1061	0.5264	1.75 (0.89, 3.45)	0.0956	0.5264
<65% normal tails[a]	Reference	1.70 (0.70, 4.12)	0.546	0.8659	2.06 (0.89, 4.76)	0.1637	0.573
Concentration <15 million/mL[a]	Reference	0.67 (0.26, 1.71)	0.6366	0.8659	0.73 (0.30, 1.78)	0.5254	0.8659
Volume <1.5 mL[a]	Reference	0.68 (0.34, 1.36)	0.6255	0.8659	0.52 (0.24, 1.13)	0.0775	0.5264
Count <60 million[a]	Reference	0.73 (0.38, 1.41)	0.8407	0.9416	0.73 (0.36, 1.48)	0.5325	0.8659
>5% megaloheads[b]	Reference	--			--		
>5% Microheads[a]	Reference	1.06 (0.25, 4.44)	0.7113	0.8659	0.73 (0.14, 3.71)	0.7038	0.8659
>35% tapered heads[a]	Reference	0.74 (0.36, 1.53)	0.2072	0.6073	1.18 (0.59, 2.37)	0.6579	0.8659
>5% bicephalic[b]	Reference	1.93 (0.18, 20.91)	0.5703	0.8659	0.97 (0.06, 14.80)	1	1
>10% amorphous heads[c]	Reference	2.06 (0.76, 5.54)	0.1128	0.5264	0.95 (0.38, 2.35)	0.6971	0.8659

[a] adjusted for age, race, income, smoking status, and body mass index (BMI)

[b] adjusted for age, income, and BMI (race and smoking status removed due to collinearity)

[c] adjusted for age, race, income, and BMI (smoking status removed due to collinearity)

GM: geometric mean, PR: prevalence ratio, FDR: False Discovery Rate