Association between adverse nutrition status by BMI and increased time-to-pregnancy in planed pregnancy couples: A cohort study in Guangzhou, China

Yuxian Zhang
Guangzhou Baiyun District Maternal and Child Health Hospital
Dongling Gu
Guangzhou Baiyun District Maternal and Child Health Hospital
Yanyuan Xie
Guangzhou Baiyun District Maternal and Child Health Hospital
Bing Li (pumpli587@163.com)
Guangdong women and children hospital

Research Article

Keywords: Infertility, Body mass index, time-to-pregnancy, NFPCP, cohort study

Posted Date: January 29th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3870307/v1

Additional Declarations: No competing interests reported.

Abstract

Background

This study addresses China's low fertility and aging issues by examining the impact of overweight and obesity on fertility. Given inconsistent results in previous research, mostly focused on females, our study targets couples in Guangzhou. We investigate the relationship between Body Mass Index (BMI) and Time to Pregnancy (TTP) to provide evidence-based strategies for enhancing reproductive outcomes in China.

Methods

This cohort study, utilizing the National Free Pre-pregnancy Checkups Project (NFPCP), employs a Cox regression model to assess the correlation between different BMI categories and TTP. Heatmaps are utilized to investigate the association between various BMI combinations of couples and TTP. Additionally, we use Restricted Cubic Spline (RCS) curves to explore the non-linear relationship between male and female BMI and TTP.

Results

The results showed that overweight and obese females (fecundability ratios (FR)0.783, 95%CI 0.644,0.954) and males (FR0.857, 95%CI 0.758,0.970) had longer TTP compared with normal weight, regardless of controlled covariates, while underweight females and males also had longer TTP, but the difference was not statistically significant (P > 0.05). Among all BMI combinations, couples in the overweight and obese groups had the lowest fertility, with a 34% decrease in fertility (TTP) compared to couples in the normal BMI combination (FR0.66; 95% CI 0.50,0.85). After adjusting for all covariates in the RCS model, female BMI surpassing 23.65 and male BMI within the range of 23.4 to 29.4continued to indicate a decrease in fertility (FR less than 1) with statistical significance.

Conclusions:

Elevated BMI, both in females and males, emerges as a significant predictor of prolonged TTP.

Background

The increasing global challenges of low fertility and aging underscore a growing concern, particularly in China. According to the key metrics of China's seventh population census in 2021, the total fertility rate was exceptionally low at 1.30 in 2020, revealing a substantial deficit compared to the population replacement level of 2.1[1]. Simultaneously, the percentage of individuals aged over 60 and 65 reached 18.7% and 13.5%, marking a respective increase of 5.44% and 4.6% over the past decade [2]. Recent epidemiological surveys indicate a declining trend in the fertility of women of childbearing age. A survey involving 10,742 Chinese women preparing for pregnancy revealed a 25% incidence of infertility, indicating a youthful and upward trend [3]. Infertility can lead to a cascade of adverse consequences for individuals, families, and society [4], necessitating an urgent exploration of factors contributing to delayed or impaired fertility. Scholars in public health advocate the concept of "Time to Pregnancy (TTP)," denoting the duration for a woman to prepare and successfully conceive, with variations between couples [5]. A shorter TTP correlates with higher fertility. In comparison to other biological indicators, TTP is deemed a more objective and practical measure for evaluating fertility. Moreover, the study uncovered that a prolonged TTP adversely impacts the psychological well-being of couples, pregnancy complications, and the health of newborns and fetuses [6–8].

Simultaneously, China grapples with growing concerns regarding the rising prevalence of overweight and obesity. Over the last four decades, China has witnessed a swift escalation in its overweight and obese population. Based on Chinese criteria, the most recent prevalence rates of overweight and obesity among adults (≥ 18 years old) in China, recorded from 2015 to 2019, were 34.3% and 16.4%, respectively [9]. Another survey revealed that the prevalence of underweight among Chinese women has surged to 7.8% [10]. This intricate interplay of demographic shifts poses significant challenges to public health, urging a nuanced exploration of factors influencing reproductive outcomes.

The body mass index (BMI) is a measure of body mass (kg)/height^2 (m^2), used to indirectly assess the body's fat content. It is a widely used indicator internationally for measuring and diagnosing overweight and obesity, and it has been recognized as a potential contributor to fertility outcomes. The association between BMI and fertility has undergone extensive study in recent years. Most studies concentrate on women, and the results consistently associate higher BMI with lower fertility [11–14]. Some studies indicate that women with a low body mass index have a higher risk of infertility, and at higher BMI levels, there are no significant differences in infertility risk [15]. Moreover, other studies suggest no difference in reproductive ability among underweight, overweight/obese, and normal weight women [16]. The research on the relationship between BMI and fertility in males primarily focuses on the association between BMI and semen. There is relatively little research on the relationship between male BMI and TTP. A meta-analysis focusing on overweight and obese males suggested that an increase in male BMI may negatively impact pregnancy [17]. Some studies also suggest that underweight males may reduce sperm quality and prolong TTP [18]. While the influence of individual BMI on fertility has been explored, limited attention has been given to the potential joint effects of couples' BMI on TTP. In studies that included both male and female BMI for analysis, the results were inconsistent [19–21].

Understanding the association between the BMI of couples and TTP is crucial for informing public health interventions and improving reproductive planning strategies. However, limited research has specifically focused on the influence of the BMI of couples on TTP, especially in the context of China, where cultural and societal factors may play a significant role. Guangzhou, as an international mega-city, a national central city, and a core city in the Guangdong-Hong Kong-Macao Greater Bay Area, possesses a highly representative population structure and pattern within the Pearl River Delta region [22]. The National Free Pre-pregnancy Checkups Project (NFPCP) is a national preconception healthcare service in China. It aims to provide free preconception health examinations, counseling, and follow-up of pregnancy outcomes for reproductive-aged couples planning to conceive [23]. NFPCP provides an opportune platform to study the intersection of low fertility, aging, and the impact of overweight and obesity on reproductive outcomes. This cohort study aims to explore the association between the BMI of couples and TTP in Guangzhou through NFPCP. Understanding how the comprehensive BMI of couples affects the time to reach pregnancy is crucial for developing public health strategies and interventions. The findings of this study will offer evidence-based recommendations for healthcare professionals, policymakers, and individuals seeking to optimize their reproductive health.

In summary, comprehending the association between the BMI of couples and TTP is essential for addressing the increasing burden of infertility in China. A comprehensive analysis of this topic will contribute to the existing literature and inform public health strategies aimed at improving reproductive outcomes.

Materials and methods

Data source and sample design

In Guangzhou, all residents planning for pregnancy are eligible to participate in the NFPCP, not limited to rural populations. A retrospective cohort study was conducted at Guangzhou Baiyun District Maternal and Child Health Hospital. The hospital is the largest designated institution for NFPCP in Guangzhou, conducting more than 10,000 pairs of pre-pregnancy examinations annually, accounting for over 13.5% of Guangzhou. Based on the designed follow-up of the NFPCP [23, 24], we incorporated a follow-up visit 13–15 months after the examination. This focused on inquiring whether the woman persisted in preparing for pregnancy after participating in the pre-pregnancy examination, including details on her diet, sleep, and exercise during the preparation period. This study received approval from the Medical Ethics Committee at Guangzhou Baiyun District Maternal and Child Health Hospital. Every participant provided written informed consent before enrolling in the study. This study is registered with the China Clinical Trials Registry (www.clinicaltrials.gov), under the registration number ChiCTR2300068809, with the initial trial registration on 01/03/2023.

Population

In this study, we selected couples who participated in the NFPCP from January 2022 to June 2022 as the research subjects. At the 13th to 15th month after the examination, we conducted telephone follow-ups to inquire about pregnancy preparation and subsequent pregnancy. We also tracked the pregnancy outcomes of pregnant women. The inclusion criteria were (1) Couples with a female partner aged between 20 and 49 and a male partner aged 22 or older; (2) Couples who were not pregnant at the time of examination; (3) Both couples reported being ready to conceive. The exclusion criteria were (1) Couples with a female partner positive for cytomegalovirus or Toxoplasma gondii IgM antibody, or if one of the couples had syphilis, HIV, or other diseases requiring treatment to delay the pregnancy plan; (2) Those with missing data on height or weight; (3) One of the couples did not agree to cooperate with the survey or to participate in this study; (4) Couples who were pregnant during the month were examined; (5) Pregnancy using assisted reproductive technology. After applying the inclusion and exclusion criteria, a total of 1684 couples were enrolled (Fig. 1).

Exposures and outcome

In this study, BMI was treated as an exposure variable. BMI was calculated as the body mass in kilograms divided by height in meters squared. According to the guidelines of the Chinese Working Group on Obesity (WGOC), the BMI threshold is defined as follows: underweight < 18.5 kg/m^2, normal weight 18.5–23.9 kg/m^2, overweight 24-27.9 kg/m^2, and obesity ≥ 28 kg/m^2. BMI was categorized into three groups: "Underweight," "Normal weight," and "Overweight and Obese".

The primary outcome was TTP.

(1) TTP for pregnant couples was calculated as (last menstrual date before pregnancy - last menstrual date at examination)/30 + 1;

(2) TTP for unpregnant couples was calculated as (Last menstrual date at follow-up - Last menstrual date at examination)/30.

The calculated TTP is reported with one decimal place and without rounding. If the couple confirms pregnancy within the second month and 15 days, it is recorded as pregnancy within the third month by adding 1 at the end of the formula. For couples who have not become pregnant within one year of follow-up, if it is confirmed that they are not pregnant during the second month and 15 days of follow-up, we can only determine if they are not pregnant within the second month, but not whether they can become pregnant within the third month. Therefore, for couples who are not pregnant, 1 is not added at the end of the TTP formula. If the couple experiences an interrupted pregnancy during pregnancy preparation, the time not preparing for pregnancy will be subtracted when calculating TTP. Additionally, in this study, self-reported pregnancies were all clinically confirmed through testing in the hospital.

Covariates

Variable selection was based on identifying variables with a known or suspected effect on the outcome of interest and/or showing P < 0.05 on univariable analysis. The covariates for this study included age, occupation, tobacco exposure (no, yes), regular menstruation (no, yes), poor sleep (no, yes), sleep time, frequent eating of takeaway (no, yes), regular intake of nutritional supplements (no, yes), and exercise frequency. All covariates pertain to the preconception period. The age of the couples was recorded at the time of their participation in the examination or when they started preparing for pregnancy after the examination. Occupation was categorized as “Business”, “Farmer”, “Housework”, “Services”, “Teacher/Civil servant/Office clerk”, “Worker”, or “Others”. Tobacco exposure was defined as active smoking or exposure to passive smoking for an average of 5 minutes or more per day. Regular menstruation status was determined through the doctor's inquiry and judgment during the examination. The study also considered the wife’s sleep situation during pregnancy preparation, and professionals inquired about frequent difficulties falling asleep or poor sleep quality. Additionally, we inquired about the time of falling asleep during the preparation period. Eating takeaway frequently was defined as once or more a day, and taking in nutritional supplements was defined as regularly supplementing with nutrients other than folic acid, such as vitamins, DHA, bird's nest, sea cucumber, etc. Exercise frequency referred to the frequency of moderate physical activity (exceeding 30 minutes each time) per week, categorized as “1–3 times per week”, “>3 times per week”, or “<1 time per week).

Statistical analysis

EpiData (version 3.1) was utilized for data input, and R (version 4.0.0) was employed for statistical analysis. Group differences were compared using the $\chi 2$ test (for categorical variables), the Wilcoxon rank-sum test (for non-normally distributed continuous variables), and analysis of variance (for normally distributed continuous variables). Continuous variables were described using the mean and standard error, while categorical variables were described as frequency and percentages. Multiple imputation was performed to mitigate sample size reduction due to missing covariates. We used Cox regression models to assess the correlation between different BMI and TTP, expressing the relationship with fecundability ratios (FR) values and 95% confidence intervals (95% CI). FR > 1 indicates a shorter TTP and increased fertility; FR < 1 indicates a longer TTP and decreased fertility. In the analysis, we developed three models: Model I without any adjustment, Model II adjusted for age, and Model III adjusted for all variables. In the Cox regression model, we also explored the multiplicative interactions between the BMI of couples. The assumption of equal proportional hazards for covariates in the regression model was validated using the Schoenfeld residual method. Additionally, we used restricted cubic spline (RCS) curves to investigate the nonlinear relationship between male and female BMI and TTP. Selecting the number of nodes for RCS using the Akechi information criterion (AIC). In the spline models, adjustments were made for all covariates.

Furthermore, we utilized heat maps to explore the TTP of couples with different BMI combinations while controlling for all variables. Finally, sensitivity analyses were conducted to explore whether live birth, chronic diseases, or polycystic ovary syndrome (PCOS) status impacted the findings. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

The 1684 couples included in the study contributed to 11973 cycles and 1127 pregnancies. The average pre-pregnancy BMI of the female and male partners was 20.77 (SD: 2.86) and 23.63 (SD: 3.34), respectively. The distribution of underweight (UW), normal weight (NW), and overweight and obese (OW/OB) in the female partners before pregnancy was 326 (19.3%), 1147 (68.1%), and 211 (12.5%), respectively; while in the male partners, it was 74 (4.4%), 1684 (53.0%), and 718 (42.6%), respectively. The median TTP for female UW, NW, and OW/OB groups were 7.4, 7.3, and 10.5, respectively, while for males they were 7.2, 7.0, and 8.4, respectively (Fig. 2). Table 1 displays the demographic characteristics of couples included in the BMI stratification. Within diverse BMI groups among females, significant statistical differences emerge in the spouse's BMI, female age, proportion of regular menstrual cycles, spouse's age, and the prevalence of tobacco exposure in spouses. Conversely, among males in distinct BMI categories, notable distinctions manifest in the spouse's BMI, male age, and spouse's age.

Table 1
Demographic characteristics of couples included in this study, stratified by BMI categories.

	Female BMI				Male BMI			
Characteristics	**Underweight (n = 326)**	**Normal weight (n = 1147)**	**Overweight and obese (n = 211)**	***P* value**	**Underweight (n = 74)**	**Normal weight (n = 892)**	**Overweight and obese (n = 718)**	***P* value**
BMI (mean (SD))	17.54 (0.73)	20.66 (1.39)	26.37 (2.51)	< 0.001	17.69 (0.61)	21.75 (1.46)	26.56 (2.62)	< 0.001
Spouse's BMI (mean (SD))	23.09(3.28)	23.58(3.21)	24.70(3.89)	< 0.001	19.75(2.64)	20.48(2.59)	21.23(3.11)	< 0.001
Age (mean (SD))	27.97 (3.31)	28.86 (3.49)	29.38 (4.28)	< 0.001	28.74 (3.68)	30.34 (4.13)	30.84 (4.75)	< 0.001
Spouse's Age (mean (SD))	29.54(3.82)	30.59(4.43)	31.45(4.90)	< 0.001	27.32(2.74)	28.61(3.50)	29.09(3.72)	< 0.001
Occupation (%)				0.195				0.094
Business	12 (3.7)	66 (5.8)	18 (8.5)		9 (12.2)	108 (12.1)	100 (13.9)	
Farmer	2 (0.6)	12 (1.0)	6 (2.8)		2 (2.7)	14 (1.6)	7 (1.0)	
Housework	9 (2.8)	34 (3.0)	7 (3.3)		2 (2.7)	9 (1.0)	6 (0.8)	
Services	52 (16.0)	207 (18.0)	38 (18.0)		22 (29.7)	154 (17.3)	114 (15.9)	
Teacher/ Civil servant/Office clerk	118 (36.2)	420 (36.6)	72 (34.1)		11 (14.9)	246 (27.6)	213 (29.7)	
Worker	34 (10.4)	88 (7.7)	16 (7.6)		10 (13.5)	129 (14.5)	95 (13.2)	
Others	99 (30.4)	320 (27.9)	54 (25.6)		18 (24.3)	232 (26.0)	183 (25.5)	
Spouse's Occupation (%)				0.048				0.137
Business	31 (9.5)	158 (13.8)	28 (13.3)		5 (6.8)	51 (5.7)	40 (5.6)	
Farmer	2 (0.6)	15 (1.3)	6 (2.8)		1 (1.3)	12 (1.3)	7 (1.0)	
Housework	2 (0.6)	11 (1.0)	4 (1.9)		1 (1.3)	30 (3.4)	19 (2.6)	
Services	56 (17.2)	195 (17.0)	39 (18.5)		13 (17.6)	142 (15.9)	142 (19.8)	
Teacher/ Civil servant/Office clerk	82 (25.2)	340 (29.6)	48 (22.7)		20 (27.0)	311 (34.9)	279 (38.9)	
Worker	52 (16.0)	150 (13.1)	32 (15.2)		5 (6.8)	79 (8.9)	54 (7.5)	
Others	101 (31.0)	278 (24.2)	54 (25.6)		29 (39.2)	267 (29.9)	177 (24.7)	
Tobacco exposure = yes (%)	15 (4.6)	51 (4.4)	10 (4.7)	0.979	31 (41.9)	268 (30.0)	243 (33.8)	0.050
Spouse's Tobacco exposure = yes (%)	104 (31.9)	347 (30.3)	91 (43.1)	0.001	6 (8.1)	37 (4.1)	33 (4.6)	0.286
Regular menstruation = yes (%)	281 (86.2)	1015 (88.5)	167 (79.1)	0.001				

	Female BMI				Male BMI			
Characteristics	**Underweight (n = 326)**	**Normal weight (n = 1147)**	**Overweight and obese (n = 211)**	***P* value**	**Underweight (n = 74)**	**Normal weight (n = 892)**	**Overweight and obese (n = 718)**	***P* value**
Poor sleep = yes (%)	48 (14.7)	159 (13.9)	29 (13.7)	0.918				
Sleep time (mean (SD))	23.59 (0.92)	23.64 (0.94)	23.74 (1.05)	0.230				
Eating takeaway frequently = yes (%)	88 (27.0)	346 (30.2)	69 (32.7)	0.343				
Taking in nutritional supplements = yes (%)	107 (32.8)	322 (28.1)	53 (25.1)	0.119				
Exercise frequency (%)				0.095				
1–3 times per week	110 (33.7)	424 (37.0)	66 (31.3)					
>3 times per week	41 (12.6)	189 (16.5)	37 (17.5)					
<1 time per week	175 (53.7)	534 (46.6)	108 (51.2)					

The association between pre-pregnancy BMI and TTP

Three Cox logistic regression models were constructed to investigate the potential impact of couples' BMI on TTP. Table 2 presents the FRs and 95% CIs for the association between different pre-pregnancy BMI and TTP in the three regression models. The results indicated that in models 1, 2, and 3, overweight and obese females (FR0.741, 95% CI 0.610, 0.899; FR0.764, 95% CI 0.629, 0.927; FR0.783, 95% CI 0.644, 0.954) and males (FR0.822, 95% CI 0.728, 0.929; FR0.843, 95% CI 0.746, 0.953; FR0.857, 95% CI 0.758, 0.970) experienced longer TTP compared with normal weight, irrespective of controlled covariates. Conversely, underweight females and males also exhibited longer TTP, but the difference was not statistically significant (P > 0.05). Additionally, the three Cox regression models explored the multiplicative interaction between BMI in females and males, and no statistical significance was observed (P > 0.05).

Table 2
Association between pre-pregnancy BMI and TTP in females and males, Cox regression analysis.

	FR (95%CI), *P* value		
	Model1[1]	**Model2**[2]	**Model3**[3]
Female BMI			
Normal weight	Reference	Reference	Reference
Underweight	0.975(0.839, 1.132) 0.737	0.941(0.810,1.093) 0.424	0.931(0.800,1.084) 0.357
Overweight and obese	0.741 (0.610,0.899) 0.002	0.764(0.629,0.927) 0.006	0.783(0.644,0.954) 0.015
Male BMI			
Normal weight	Reference	Reference	Reference
Underweight	1.000(0.753,1.330) 0.967	0.931(0.699,1.239) 0.624	0.922(0.689,1.233) 0.584
Overweight and obese	0.822(0.728,0.929) 0.002	0.843(0.746,0.953) 0.006	0.857(0.758,0.970) 0.015
Note: FR, fecundability ratio; 95% Cl, 95% confidence interval.			

[1] Model 1: No covariates were adjusted.

[2] Model 2: Adjusted for couples' age.

[3] Model 3: Adjusted for couples' age, occupation, tobacco exposure, and females' regular menstruation, poor sleep, sleep time, eating takeaway frequently, taking in nutritional supplements, exercise frequency.

Heat map of association analysis between different BMI combinations and TTP

We combined the BMI of three different categories for females and males into nine different combinations and explored their additive interaction in the fully adjusted Cox regression model (Fig. 3). Across all BMI combinations, couples in the overweight and obese groups exhibited the lowest fertility, experiencing a 34% decrease in fertility (TTP) compared to couples in the normal BMI combination (FR0.66; 95% CI 0.50, 0.85).

Restricted cubic spline model of the association between BMI and TTP in females and males

We utilized Restricted Cubic Splines (RCS) to simulate and model the relationship between BMI and TTP in both female and male participants (Fig. 4). For the female BMI RCS model, three nodes were selected, and for the male BMI RCS model, four nodes were chosen based on the AIC. In all four RCS models, the dose-response relationship between BMI and TTP exhibited an approximately linear trend (all P-values for non-linearity > 0.05). In the unadjusted covariate RCS model, female BMI exceeding 21.05 and male BMI ranging from 23.4 to 30.9 were associated with a decrease in fertility (FR less than 1), and these associations were statistically significant. After adjusting for all covariates in the RCS model, female BMI surpassing 23.65 and male BMI within the range of 23.4 to 29.4 continued to indicate a decrease in fertility (FR less than 1) with statistical significance.

The black horizontal dashed line indicates the hazard ratio = 1.

Sensitivity analyses

In the sensitivity analysis, the association between BMI and TTP remained almost unchanged after excluding participants who self-reported having chronic diseases, PCOS, and retaining those with live birth outcomes (excluding biochemical pregnancies, abortions or stillbirths) (Table 3).

Table 3
Association between pre-pregnancy BMI and TTP in sensitivity analyses

	Excluding those who self-reported chronic diseases (n = 1418)			**Excluding those who self-reported PCOS (n = 1611)**		
	Model1[1]	**Model2[2]**	**Model3[3]**	**Model1[1]**	**Model2[2]**	**Model3[3]**
Female BMI						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Underweight	0.973(0.826–1.145)0.741	0.933(0.791–1.099)0.404	0.950(0.805–1.122)0.547	0.992(0.853–1.153)0.916	0.955(0.821–1.111)0.548	0.925(0.793–1.077)0.315
Overweight and obese	0.698(0.562–0.867)0.001	0.705(0.568–0.876)0.002	0.727(0.583–0.906) 0.004	0.772(0.633–0.943)0.011	0.799(0.655–0.976)0.028	0.788(0.643–0.965)0.021
Male BMI						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Underweight	1.020(0.753–1.382)0.897	0.937(0.691–1.272)0.678	0.926(0.679–1.264)0.630	0.965(0.724–1.286)0.808	0.985(0.966–1.004)0.448	0.890(0.664–1.194)0.438
Overweight and obese	0.827(0.724–0.945)0.005	0.851(0.744–0.972)0.02	0.874(0.763–0.999)0.049	0.829(0.733–0.937)0.003	0.851(0.753–0.963)0.011	0.868(0.766–0.983)0.026
	Retaining those with live birth outcomes (n = 1541)					
	Model1[1]	**Model2[2]**	**Model3[3]**			
Female BMI						
Normal weight	Reference	Reference	Reference			
Underweight	0.981(0.838–1.149)0.813	0.942(0.803–1.104)0.458	0.941(0.801–1.105)0.456			
Overweight and obese	0.729(0.592–0.899)0.003	0.752(0.610–0.928)0.008	0.770(0.622–0.952)0.016			
Male BMI						
Normal weight	Reference	Reference	Reference			
Underweight	1.024(0.757–1.387)0.876	0.938(0.692–1.272)0.682	0.927(0.681–1.263)0.632			
Overweight and obese	0.830(0.729–0.946)0.005	0.859(0.754–0.979)0.023	0.864(0.757–0.986)0.030			

Discussion

In this cohort study, 1,684 couples were included, with 1,127 achieving pregnancy, constituting 67.0% of the total couples included. The observed pregnancy rate surpassed that of other NFPCP-related studies[23, 25], potentially attributed to excluding couples discontinuing efforts to conceive after the examination in our inclusion analysis. In three distinct Cox regression models, both overweight and obesity in both males and females were linked to prolonged TTP compared to normal weight. Nonetheless, no statistically significant differences in TTP were observed between underweight and normal weight individuals. The third model underwent meticulous adjustments for covariates (including age, occupation, tobacco exposure, and various lifestyle factors), underscoring the robustness of this study. Despite comprehensive adjustments, BMI remained a persistent and significant predictor of TTP, indicating an independent influence on fecundability. In the sensitivity analysis, we excluded couples with self-reported PCOS, chronic diseases, and non-viable pregnancy outcomes individually. Despite these exclusions, TTP remained prolonged for overweight and obese couples, affirming the robustness of the results. Moreover, in the Cox regression models, no multiplicative interaction effect was observed between male and female BMI. Simultaneously, we aggregated three BMI categories for women and men into nine combinations. In a Cox regression model adjusted for confounding factors, we identified that, among all BMI combinations, the fertility of overweight and obese groups decreased by 34% compared to the normal BMI combination. Currently, limited studies have delved into the concurrent examination of marital BMI and fertility. A study from the Danish National Birth Cohort suggested that the risk of low fertility is linked to overweight and obesity for both males and females, particularly in couples where both partners are overweight[26], aligning with our research findings. A retrospective cohort study from China indicates that, in comparison to women with a normal pre-pregnancy BMI, women who were overweight or obese before pregnancy experienced a prolonged TTP and an elevated risk of impaired fertility. However, no correlation was found between TTP and male BMI[21]. Another study from China focusing on couples experiencing their first pregnancy suggests that underweight, overweight, or obese status in women, and underweight status in men, were associated with prolonged TTP[27]. A cohort study from the United States revealed that, when modeled separately, the BMI of male and female partners exhibited no association with TTP. Nevertheless, in couples where both partners were classified as obese class II, fertility reduction led to a longer TTP compared to couples with a normal BMI[19–21]. A cohort study from Norway, employing logistic regression analysis, supported a J-shaped association between BMI and reduced fertility, indicating that both higher and lower BMIs are linked to a greater risk of reduced fertility[19]. Discrepancies might stem from variations in BMI classification standards, racial diversity among the study population, and differences in sample sizes compared to the aforementioned research.

In the adjusted RCS analysis, the dose-response relationship between BMI and TTP seems to exhibit a linear trend. For females with a BMI exceeding 23.65 and males with a BMI ranging from 23 to 29.4, TTP is significantly prolonged, suggesting that higher BMI negatively impacts fertility for both genders. However, when male BMI exceeds 29.4, a significant impact on fertility was not observed. This observation could be attributed to the relatively small sample size of obese males in this study.

Overweight, obesity, and infertility have always been global concerns, and their interrelationships are worth exploring. In investigating the mechanism of female infertility, some studies suggest that obesity-induced systemic and tissue-specific chronic inflammation and oxidative stress can impair the meiosis and cytoplasmic maturation of oocytes[28–30], thereby reducing their developmental ability for fertilization and pre-implantation embryo development[31]. Additionally, some studies propose that the impact of obesity on female fertility is primarily attributed to alterations in the function of the hypothalamic-pituitary-ovarian (HPO) axis. Obesity is often associated with elevated circulating insulin levels, subsequently leading to increased ovarian androgen production[32]. Excessive adipose tissue is responsible for aromatizing these androgens into estrogens, inducing a negative feedback loop in the HPO axis and affecting the production of gonadotropins[33], thereby causing ovulatory dysfunction and menstrual irregularities. In males, a meta-analysis suggests a significant correlation between increased BMI and decreased seminal volume, sperm count, concentration, and viability[34]. Additionally, in animal studies, obesity is correlated with increased sperm DNA damage, but findings in human studies are inconsistent in this regard[35]. The abnormal lipid profile in obese males may lead to testicular oxidative stress, which is a common pathway for disruption in sperm function[36]. Some studies suggest that in an obese environment, the inflammatory response triggered by excessive accumulation of abdominal fat may lead to hypothalamic inflammation, thereby influencing the release of hormones from the hypothalamus and causing dysregulation of the HPG axis[37]. Furthermore, the mechanisms linking male obesity to infertility may also involve endocrine disruptions, erectile dysfunction, and physical disorders such as high scrotal temperature[38, 39]. Despite the potential existence of these mechanisms, further research is needed to elucidate the underlying molecular pathways linking BMI to infertility. Developing effective interventions for preventing and treating infertility associated with overweight and obesity also requires additional investigation. Currently, correcting obesity is considered a potential way to reverse the impact on the male reproductive system. This is achieved through improving nutritional quality, incorporating appropriate exercise, considering micronutrients, and supplementing with light therapy[40]. Achieving optimal weight or meaningful weight loss/fat reduction before conception may be a targeted intervention to improve female fertility[41]. Lifestyle interventions for obese and infertile women can enhance female reproductive function[42]., thereby improving infertility. For couples of reproductive age, controlling preconception BMI is crucial; doctors should provide weight-related health guidance to couples preparing for pregnancy during pre-pregnancy counseling.

Strengths and limitation

Our research presents several distinct advantages. Firstly, unlike the previous NFPCP, which solely targeted rural populations, our study extended its scope beyond registered residency limitations, encompassing all permanent residents. Secondly, our investigation delved into both male and female BMI, constructing diverse models by adjusting for various variables. Moreover, we employed sensitivity analysis to assess the robustness of our findings. Thirdly, we explored the multiplicative and additive effects of male and female BMI, utilizing restrictive cubic splines to identify specific BMI thresholds associated with reduced fertility in both genders. This nuanced approach enriched our comprehension of the intricate relationship between body mass index and TTP. Lastly, in contrast to conventional NFPCP projects, our study introduced additional variables pertaining to TTP, encompassing aspects such as a woman's sleep habits, frequency of takeout consumption, nutrient intake, and exercise frequency during pregnancy preparation.

However, there are some limitations to our study. Firstly, potential selection bias could arise from participation in the NFPCP and its subsequent follow-ups, as individuals with diverse motivations for seeking prenatal care might differ from the general population. Secondly, self-reported covariates, such as lifestyle factors, may introduce recall bias, thereby potentially impacting the data's accuracy. Thirdly, our study established a correlation between BMI and fertility without delving into the underlying mechanisms, which presents an avenue for future research. Additionally, the limited geographical focus on Guangzhou may pose challenges to the study's external validity when extrapolating the findings to a broader Chinese population. Hence, caution is warranted in generalizing these results to a wider demographic.

Conclusions

In conclusion, our study establishes a robust link between couples' BMI and time-to-pregnancy in the urban setting of Guangzhou, China. Elevated BMI, both in females and males, emerges as a significant predictor of prolonged TTP, suggesting the need for targeted interventions to optimize reproductive outcomes. The gender-specific thresholds identified in our study provide valuable guidance for healthcare practitioners and public health initiatives aiming to improve fertility in urban Chinese populations.

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

YZ and BL designed the study. YZ collected, analyzed the data and drafted the manuscript. YX and DG collected the data and assisted in literature search. BL and DG gave suggestions, and BL revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The study was not funded by any organization.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

This study received approval from the Medical Ethics Committee at Guangzhou Baiyun District Maternal and Child Health Hospital. Every participant provided written informed consent before enrolling in the study. This study is registered with the China Clinical Trials Registry (www.clinicaltrials.gov) (registration number ChiCTR2300068809).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1. HU GWY. The Low Fertility Rate in China from the Seventh National Census. Popul J. 2022;44(06):1–14. (Chinese).
2. Tu WJ, Zeng X, Liu Q. Aging tsunami coming: the main finding from China's seventh national population census. Aging Clin Exp Res. 2022;34(5):1159–63.
3. Zhou Z, Zheng D, Wu H, Li R, Xu S, Kang Y, Cao Y, Chen X, Zhu Y, Xu S, et al. Epidemiology of infertility in China: a population-based study. BJOG: an international journal of obstetrics and gynaecology. 2018;125(4):432–41.
4. Boedt T, Vanhove AC, Vercoe MA, Matthys C, Dancet E, Lie Fong S. Preconception lifestyle advice for people with infertility. Cochrane Database Syst Rev. 2021;4(4):Cd008189.
5. Bello B, Heederik D, Kielkowski D, Wilson K. Increased time-to-pregnancy is associated with domestic work in South Africa. Reproductive health. 2016;13(1):106.
6. Thurston L, Abbara A, Dhillo WS. Investigation and management of subfertility. J Clin Pathol. 2019;72(9):579–87.
7. Magnus MC, Fraser A, Rich-Edwards JW, Magnus P, Lawlor DA, Håberg SE. Time-to-pregnancy and risk of cardiovascular disease among men and women. Eur J Epidemiol. 2021;36(4):383–91.
8. Wise LA, Mikkelsen EM, Sørensen HT, Rothman KJ, Hahn KA, Riis AH, Hatch EE. Prospective study of time to pregnancy and adverse birth outcomes. Fertil Steril. 2015;103(4):1065–1073e1062.
9. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. The lancet Diabetes & endocrinology. 2021;9(6):373–92.
10. Trends in adult. body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet (London England). 2016;387(10026):1377–96.
11. Burger T, Li J, Zhao Q, Schreiber CA, Teal S, Turok DK, Natavio M, Peipert JF. Association of Obesity With Longer Time to Pregnancy. Obstet Gynecol. 2022;139(4):554–60.
12. Loy SL, Cheung YB, Soh SE, Ng S, Tint MT, Aris IM, Bernard JY, Chong YS, Godfrey KM, Shek LP, et al. Female adiposity and time-to-pregnancy: a multiethnic prospective cohort. Hum Reprod (Oxford England). 2018;33(11):2141–9.
13. 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.
14. Tang J, Xu Y, Wang Z, Ji X, Qiu Q, Mai Z, Huang J, Ouyang N, Chen H. Association between metabolic healthy obesity and female infertility: the national health and nutrition examination survey, 2013–2020. BMC Public Health. 2023;23(1):1524.
15. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. Obstet Gynecol. 2007;110(5):1050–8.
16. Hu P, Cai C, Vinturache A, Hu Y, Gao Y, Zhang J, Lu M, Gu H, Qiao J, Tian Y, et al. Maternal preconception body mass index and time-to-pregnancy in Shanghai Women, China. Women Health. 2020;60(9):1014–23.
17. Campbell JM, McPherson NO. Influence of increased paternal BMI on pregnancy and child health outcomes independent of maternal effects: A systematic review and meta-analysis. Obes Res Clin Pract. 2019;13(6):511–21.
18. Luque EM, Tissera A, Gaggino MP, Molina RI, Mangeaud A, Vincenti LM, Beltramone F, Larcher JS, Estofán D, Fiol, de Cuneo M et al. Body mass index and human sperm quality: neither one extreme nor the other. *Reproduction, fertility, and development* 2017, 29(4):731–739.
19. Hernáez Á, Rogne T, Skåra KH, Håberg SE, Page CM, Fraser A, Burgess S, Lawlor DA, Magnus MC. Body mass index and subfertility: multivariable regression and Mendelian randomization analyses in the Norwegian Mother, Father and Child Cohort Study. Hum Reprod (Oxford England). 2021;36(12):3141–51.

20. Sundaram R, Mumford SL, Buck Louis GM. Couples' body composition and time-to-pregnancy. Hum Reprod (Oxford England). 2017;32(3):662–8.
21. Fang Y, Liu J, Mao Y, He Y, Li M, Yang L, Zhu Q, Tong Q, Zhou W. Pre-pregnancy body mass index and time to pregnancy among couples pregnant within a year: A China cohort study. PLoS ONE. 2020;15(4):e0231751.
22. Qi An Y, Qu X, Di Chen KG. Linguo Tang, Yiqun Gu,Liandong Zuo: Correlation of age, body mass index and obesity-related biochemical indexes with semen quality in males intending for a second child. Natl J Androl. 2019;25(07):595–602. (Chinese).
23. Yang Y, Guo T, Fu J, Zhao J, Wang Y, He Y, Peng Z, Zhang Y, Zhang H, Zhang Y, et al. Association of Preconception Thyrotropin Levels With Fecundability and Risk of Spontaneous Abortion in China. JAMA Netw open. 2022;5(8):e2228892.
24. Yang Y, He Y, Li Q, Wang Y, Peng Z, Xu J, Ma X. Preconception blood pressure and risk of preterm birth: a large historical cohort study in a Chinese rural population. Fertil Steril. 2015;104(1):124–30.
25. Hong X, Zhao J, Yin J, Zhao F, Wang W, Ding X, Yu H, Ma X, Wang B. The association between the pre-pregnancy vaginal microbiome and time-to-pregnancy: a Chinese pregnancy-planning cohort study. BMC Med. 2022;20(1):246.
26. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sørensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod (Oxford England). 2007;22(6):1634–7.
27. Zhang Y, Zhang J, Zhao J, Hong X, Zhang H, Dai Q, Wang Y, Yang X, Wang Q, Shen H, et al. Couples' prepregnancy body mass index and time to pregnancy among those attempting to conceive their first pregnancy. Fertil Steril. 2020;114(5):1067–75.
28. Xie F, Anderson CL, Timme KR, Kurz SG, Fernando SC, Wood JR. Obesity-Dependent Increases in Oocyte mRNAs Are Associated With Increases in Proinflammatory Signaling and Gut Microbial Abundance of Lachnospiraceae in Female Mice. Endocrinology. 2016;157(4):1630–43.
29. Nteeba J, Ortinau LC, Perfield JW 2nd, Keating AF. Diet-induced obesity alters immune cell infiltration and expression of inflammatory cytokine genes in mouse ovarian and peri-ovarian adipose depot tissues. Mol Reprod Dev. 2013;80(11):948–58.
30. Biswas SK. Does the Interdependence between Oxidative Stress and Inflammation Explain the Antioxidant Paradox? *Oxidative medicine and cellular longevity* 2016, 2016:5698931.
31. Snider AP, Wood JR. Obesity induces ovarian inflammation and reduces oocyte quality. Reprod (Cambridge England). 2019;158(3):R79–r90.
32. Rachoń D, Teede H. Ovarian function and obesity–interrelationship, impact on women's reproductive lifespan and treatment options. Mol Cell Endocrinol. 2010;316(2):172–9.
33. Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. Am J Obstet Gynecol. 2010;203(6):525–30.
34. Salas-Huetos A, Maghsoumi-Norouzabad L, James ER, Carrell DT, Aston KI, Jenkins TG, Becerra-Tomás N, Javid AZ, Abed R, Torres PJ, et al. Male adiposity, sperm parameters and reproductive hormones: An updated systematic review and collaborative meta-analysis. Obes reviews: official J Int Association Study Obes. 2021;22(1):e13082.
35. Peel A, Saini A, Deluao JC, McPherson NO. Sperm DNA damage: The possible link between obesity and male infertility, an update of the current literature. Andrology. 2023;11(8):1635–52.
36. Anupam Biswas UJADsSB. Dietary hypercholesterolemia induces oxidative stress challenging spermatogenesis in rat model: A link to possible infertility. Int J Pharm Sci Res. 2017;8(12):5065–71.
37. Castro AM, LEM-dC CA. Pantoja-Meléndez: Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Revista Médica del Hospital General de México. 2017;80(2):101–5.
38. Leisegang K, Bouic PJ, Henkel RR. Metabolic syndrome is associated with increased seminal inflammatory cytokines and reproductive dysfunction in a case-controlled male cohort. Am J reproductive Immunol (New York NY: 1989). 2016;76(2):155–63.
39. Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. Nat reviews Urol. 2010;7(3):153–61.
40. Leisegang K, Sengupta P, Agarwal A, Henkel R. Obesity and male infertility: Mechanisms and management. Andrologia. 2021;53(1):e13617.
41. Wekker V, Karsten MDA, Painter RC, van de Beek C, Groen H, Mol BWJ, Hoek A, Laan E, Roseboom TJ. A lifestyle intervention improves sexual function of women with obesity and infertility: A 5 year follow-up of a RCT. PLoS ONE. 2018;13(10):e0205934.

42. Talmor A, Dunphy B. Female obesity and infertility. Best Pract Res Clin Obstet Gynecol. 2015;29(4):498–506.

Figures

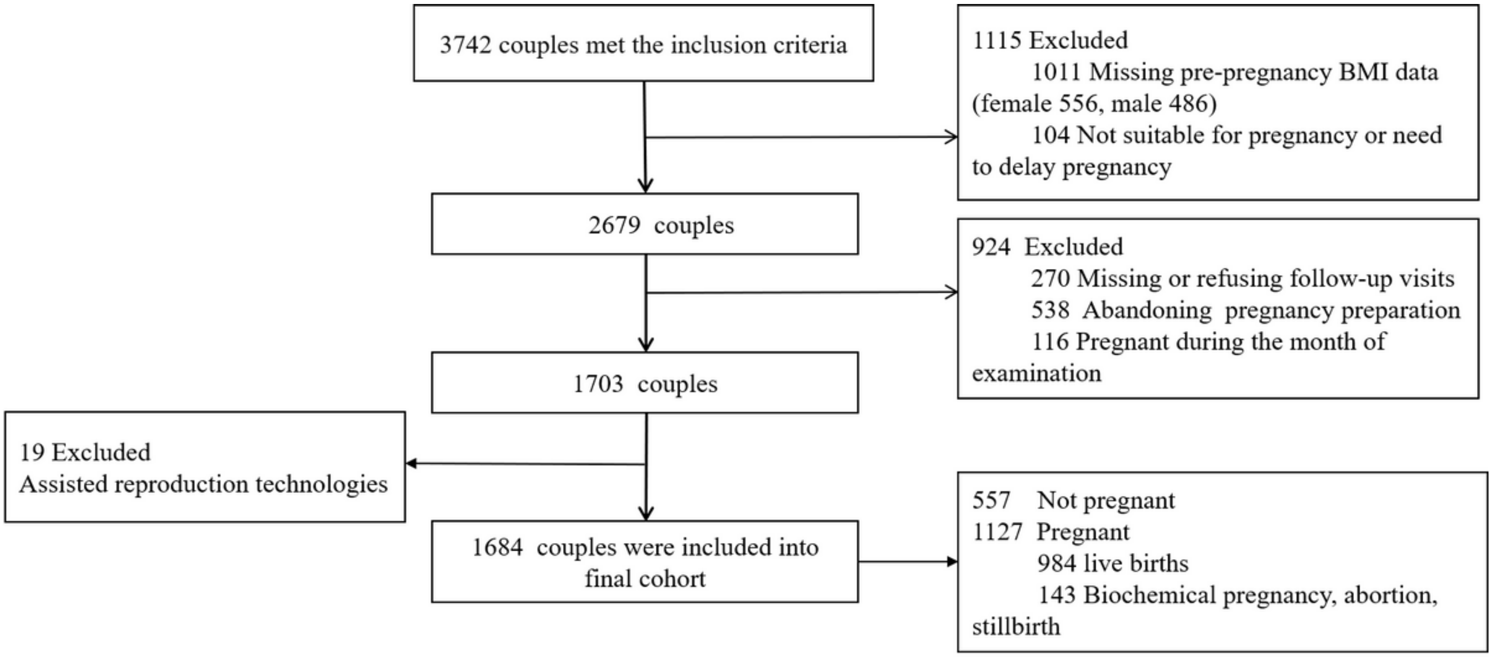

Figure 1

Flow chart of eligible participants' selection

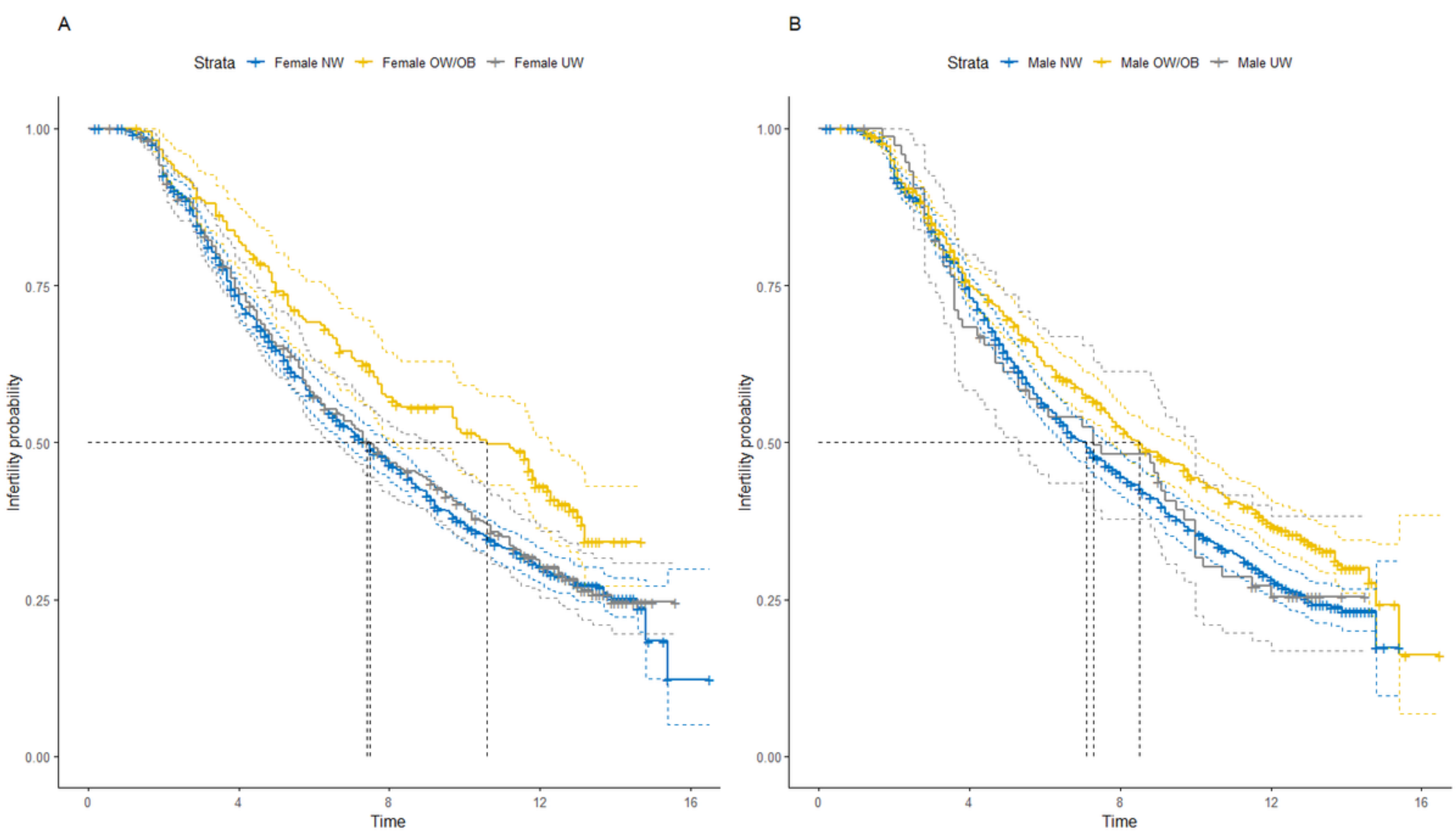

Figure 2

Survival curves for different BMI categories in females and males

Note:UW, underweight; UW, normal weight; OW/OB, overweight and obese.

A: Survival curves for different BMI categories in females

B: Survival curves for different BMI categories in males

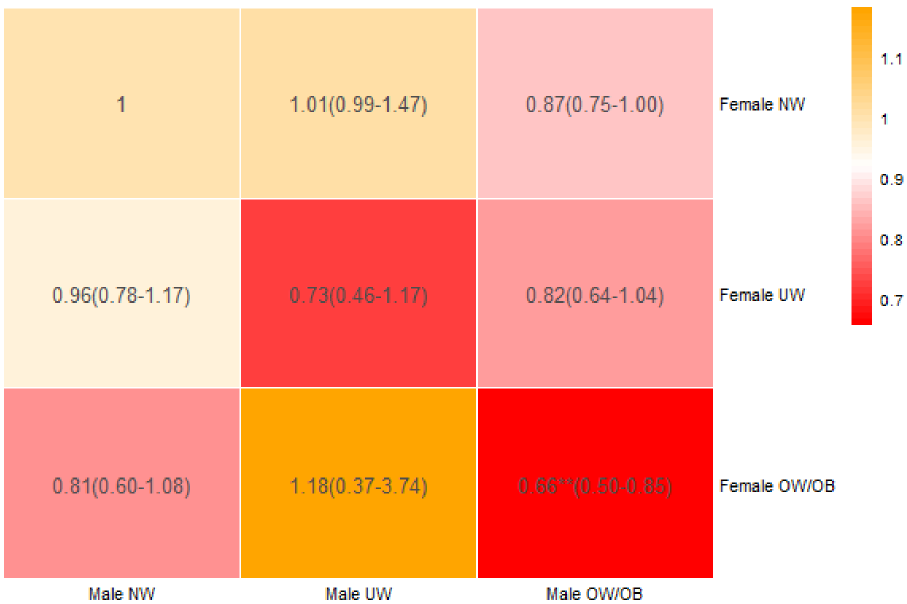

Figure 3

Heat map of association analysis between different couples' BMI combinations and TTP

Note: UW, underweight; UW, normal weight; OW/OB, overweight and obese.

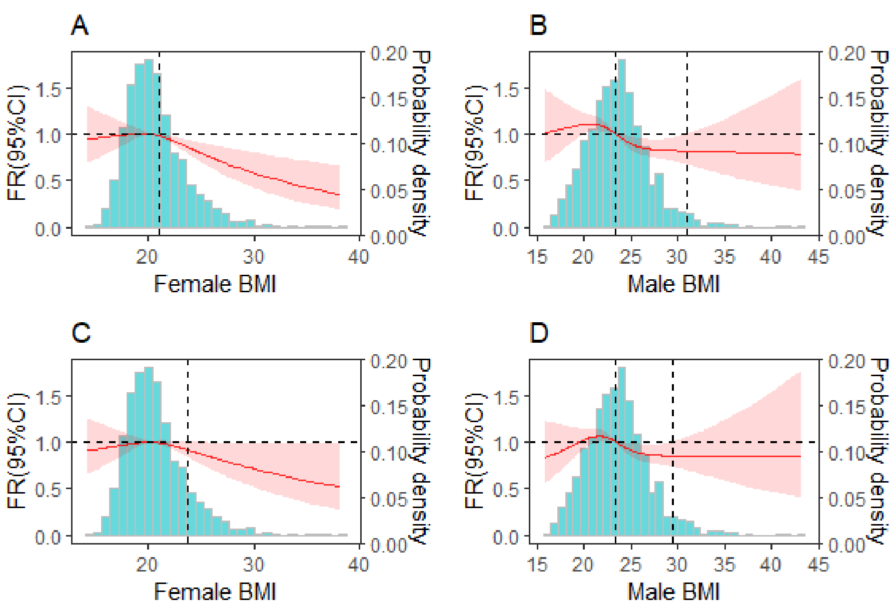

Figure 4

Restricted cubic spline model of the association between BMI and TTP in females and males

Note: FR, fecundability ratio.

A: A Restricted Cubic Spline Model for Female BMI without Adjusting for confounding Factors. P-values for non-linearity was 0.084.

B: A Restricted Cubic Spline Model for Male BMI without Adjusting for confounding Factors. P-values for non-linearity was 0.250.

C: A Restricted Cubic Spline Model for Female BMI with Adjusting for spouse BMI, couples' age, occupation, tobacco exposure, and females' regular menstruation, poor sleep, sleep time, eating takeaway frequently, taking in nutritional supplements, exercise frequency. P-values for non-linearity was 0.183.

D: A Restricted Cubic Spline Model for Male BMI with Adjusting for spouse BMI, couples' age, occupation, tobacco exposure, and females' regular menstruation, poor sleep, sleep time, eating takeaway frequently, taking in nutritional supplements, exercise frequency. P-values for non-linearity was 0.195.

The black horizontal dashed line indicates the hazard ratio = 1.