


# Association between oral contraceptive use and incident heart failure

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## Abstract

**Aims** Oral contraceptives (OCs) are widely used in women of reproductive age, but their influences on heart failure (HF) development have yet to be reported. This study was performed to assess HF risk associated with OC use.

**Methods and results** We studied women participating in the Multi-Ethnic Study of Atherosclerosis with available data on OC use. Inverse probability of treatment weighting analyses were used to reduce baseline imbalances. Cox proportional hazards models were applied to evaluate the associations of OC use and HF risk. The primary analysis comprised a total of 3594 participants [average age 62.10 (10.24) years]. During an average follow-up of 12.45 (3.75) years, 138 incident HF occurred. In unadjusted Cox model, OC use was associated with a decreased risk of HF [hazard ratio (HR) = 0.45, 95% confidence interval (CI) 0.31–0.64,  $P < 0.001$ ]. However, in multivariable-adjusted and inverse probability of treatment weighting models, the results were attenuated and became non-significant (HR = 0.96, 95% CI 0.63–1.48,  $P = 0.86$  and HR = 0.79, 95% CI 0.45–1.40,  $P = 0.43$ , respectively). Duration of OC use was not related to increased risks of HF. When stratifying HF into subtypes, similar associations were observed. In multivariable-adjusted regression models, OC use was positively associated with left ventricular end-diastolic mass [coefficient ( $\beta$ ) = 3.04,  $P = 0.006$ ] and stroke volume ( $\beta = 1.76$ ,  $P = 0.01$  for the left ventricle;  $\beta = 2.17$ ,  $P = 0.005$  for the right ventricle) but had no impact on left ventricular ejection fraction ( $\beta = 0.09$ ,  $P = 0.75$ ) and right ventricular ejection fraction ( $\beta = 0.33$ ,  $P = 0.25$ ).

**Conclusions** Oral contraceptive use in women of reproductive age does not portend increased risk of HF. However, whether the formulations or dosages differently impact this association should be further investigated.

**Keywords** Oral contraceptive; Heart failure; Cardiac function; Reproductive; Cardiovascular health

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## Introduction

The cardioprotective role of endogenous oestrogen in women has been generally accepted.<sup>1,2</sup> However, the impacts of exogenous sex hormones on cardiovascular system remain controversial.<sup>3–10</sup> Most of these studies were focusing on hormone replacement therapy in post-menopausal women,<sup>3–6</sup> while the safety of oral contraceptive (OC) use in women of reproductive age remains uncertain.

Owing to high efficacy and ease of use, OCs are frequently prescribed to women of child-bearing age. Approximately 10.7 million women of reproductive age in the USA and 104

million women worldwide use OCs as the contraception method.<sup>11,12</sup> Despite this widespread use of these agents, little is known of their influence on cardiovascular system.

It has been reported that OCs may increase blood pressure, disturb lipid metabolism, and promote volume retention,<sup>13–16</sup> most of which are cardiovascular risk factors. Although increasing number of studies have investigated the associations of OC use and cardiovascular diseases (CVDs), most were evaluating the outcome of coronary heart disease, myocardial infarction (MI), and stroke.<sup>7–10,17–20</sup> There is a paucity of research on the role of OC use in cardiac remodelling and the development of heart failure (HF). The

only study we found was a case–control study reported in 1980, showing that healthy women taking OCs did not appear to be at increased risk of abnormal ventricular volume or contraction.<sup>21</sup> However, this study was limited by small sample size and suboptimal study design. Importantly, we were unable to find any longitudinal studies relating the use of OCs to the occurrence of subsequent HF.

Therefore, the purpose of the present study was to evaluate the association between OC use and subsequent HF risk. In addition, as a secondary aim, we further examined the relationship of OC use to individual cardiac parameter assessed by magnetic resonance imaging (MRI).

## Methods

### Setting and participants

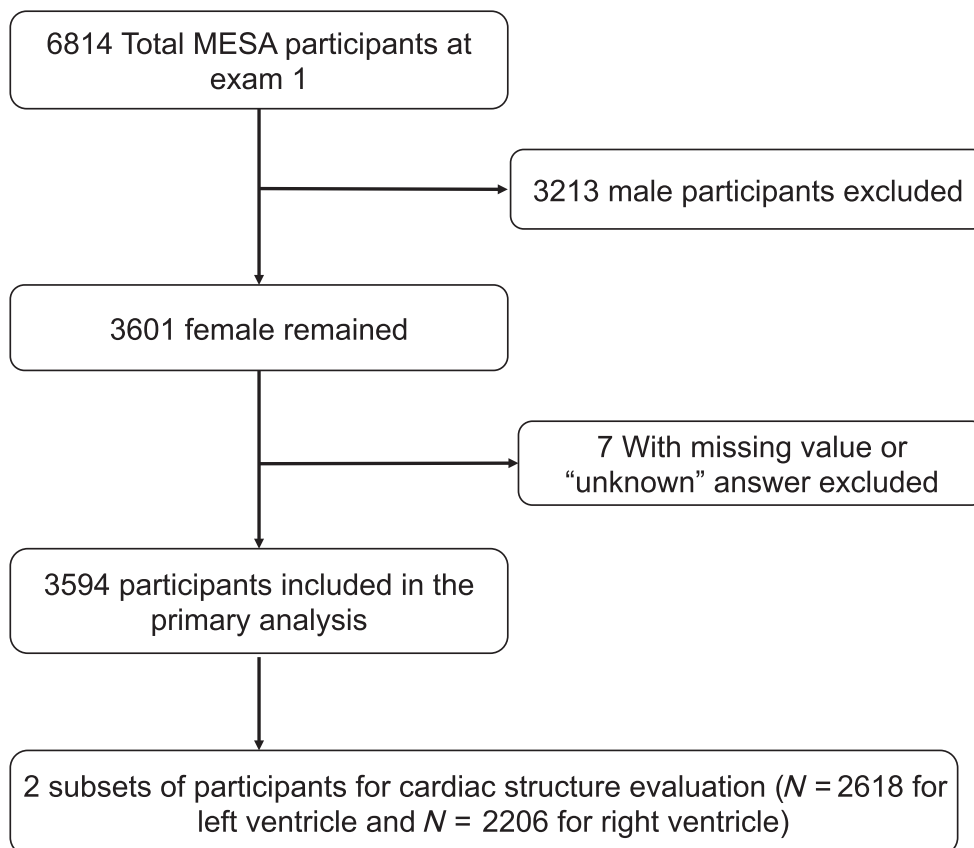
The design of the Multi-Ethnic Study of Atherosclerosis (MESA) has been described in detail previously.<sup>22</sup> Briefly, a total of 6814 participants who were aged 45 to 84 years of age and free of CVDs at baseline visit (Exam 1, 2000 to 2002)

were initially recruited from six field centres. We excluded 3213 male participants and 7 female participants with missing value or ‘unknown’ answer for OC use. The final sample size was 3594 female participants. Among these individuals, 2618 had cardiac MRIs interpretable for the left ventricle, of which 2206 were available and interpretable for the right ventricle (*Figure 1*). The study was approved by the institutional review boards from all centres. Written informed consent was obtained from all participants.

### Reproductive data

Details of women’s reproductive history were obtained from questionnaires of the medical history. We used the following variables in this study: ever use of OCs, duration of OC use, the use of hormone replacement therapy, history of breast cancer, hysterectomy, and oophorectomy, and pregnancy history. The following questions were asked, and the answers were recorded accordingly: have you ever been pregnant? Have you had a hysterectomy (surgery to remove your uterus/womb)? Have you had surgery to remove ovaries? Have you ever taken birth control pills? If yes, estimate the

**Figure 1** Flow chart of the study population. MESA, Multi-Ethnic Study of Atherosclerosis.



total number of years that you took birth control pills. Are you currently using hormone replacement therapy? Based on this information, women were grouped into treated (OC users) or untreated (non-users) groups.

## Measurements of other covariates

Demographic characteristics, lifestyle factors, and histories were collected through standardized questionnaires. We simply classified race into White or non-White in this study. History of hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and diastolic blood pressure  $\geq 90$  mmHg, self-reported hypertension, or using antihypertensive medications. History of diabetes mellitus was defined as self-reported diabetes, a fasting serum glucose  $\geq 126$  mg/dL, or use of anti-diabetic medications. Based on prior publications, education levels were regrouped into elementary school only, high school only, some college or technical school, and college completed or above.<sup>23,24</sup> Smoking status was classified as never, former, or current smoker. The amount of smoking was calculated as certain pack of cigarettes being smoked per year \* smoking years (pack-years). Alcohol drinking status was categorized into never, former, or current drinker.

Height and body weight were derived from standardized physical examination; body mass index was calculated by weight (kg) divided by square of height ( $m^2$ ). Seated resting blood pressure was measured three times, and the average of second and third measurements was used in this study. Fasting serum glucose, total cholesterol, high-density (HDL) or low-density lipoprotein cholesterol, and triglycerides were measured as previously described.<sup>22</sup>

## Outcome ascertainment and cardiac structure assessment

Participants were followed from Baseline Exam 1 until they experienced HF, MI, stroke, or death, were lost to follow-up, or until 31 December 2015. Clinical events were ascertained by telephone interviews every 9–12 months, with all events adjudicated by an independent MESA committee.<sup>22</sup> The main outcome in this study was HF, while all-cause death, total CVDs, MI, and stroke were examined as secondary outcomes. The HF diagnosis included definite or probable HF and required the symptoms of dyspnoea or oedema. More specifically, probable HF was diagnosed by a physician or using HF medications. Definite HF should be further confirmed by one or more evidence from the following results: pulmonary oedema or congestion by chest X-ray, ventricular dilation, poor left ventricular (LV) function, or LV diastolic dysfunction by echocardiography or ventriculography.<sup>25</sup> Ejection fraction measurement information was recorded for

events diagnosed as HF by MESA cardiac reviewers. Based on LV ejection fraction (LVEF) ( $\geq 50\%$  or  $< 50\%$ ), HF was further classified as either HF with preserved ejection fraction or HF with reduced ejection fraction.<sup>26,27</sup>

Cardiac MRI was performed to measure the cardiac structure, using 1.5 T whole-body magnets and with electrocardiogram gating. The MRI parameters were assessed in long-axis and short-axis images taken via a single-breath-hold sequence. Further details of the CMR methods have been described in previous publications.<sup>25,28</sup> The structural and functional measures used in this study included the LV (LVEDM) and right ventricular end-diastolic mass (RVEDM), stroke volume of the left and right ventricles, LVEF, right ventricular ejection fraction, and tricuspid annular plane systolic excursion. LVEDM, RVEDM, LV stroke volume, and right ventricular stroke volume were further divided by body surface area to calculate the corresponding index values: LV mass index, right ventricular mass index, LV stroke volume index, and right ventricular stroke volume index.

## Statistical analysis

Descriptive statistics were presented as means  $\pm$  standard deviation for continuous variables and proportions for categorical variables. Baseline characteristics of the study population were summarized and compared by using Student's *t*-test or  $\chi^2$  test.

To address the systematic differences between the two groups, we used inverse probability of treatment weighting (IPTW) analyses to reduce imbalances in measured confounders.<sup>29,30</sup> The propensity of being in the treated group (OC users) was estimated with a logistic regression model with covariates as follows: age, race, education level, family income, marital status, alcohol use, smoking status, smoking amount (pack-years), history of pregnancy (ever pregnant or not), systolic blood pressure, history of hypertension, diabetes, breast cancer, hysterectomy, or oophorectomy, and body mass index. The chosen variables were based on previous published reports and biological plausibility.<sup>20,24</sup> The estimated propensity scores were used to calculate each patient's inverse probability of being treated with OCs. Post-weighting balance in covariates between treatment groups was evaluated using the standardized difference approach. Imbalance was defined as an absolute standardized difference of  $> 10\%$ .<sup>29,30</sup>

Cox proportional hazards regression was used to examine the associated risks with OC use. We used five models with increasing degrees of adjustment to assess the associated risks: (i) non-adjusted model; (ii) age-adjusted model (adjusted for age); (iii) multivariable-adjusted model (adjusted for age, race, smoking status, education level, drinking status, history of hypertension and diabetes, ever use of hormone replacement therapy, body mass index, and fasting

serum glucose and lipid profiles); (iv) IPTW model (adjusted for IPTW); (v) adjusted IPTW model (a combination of IPTW and covariate adjustment correcting for residual imbalances after weighting, including age at first birth, race, history of breast cancer, and HDLC). We also assessed the risk of incident HF with duration of OC use, as either a continuous or categorical variable. On the basis of previous literature, we categorized the duration into five groups (never use and 0–5, 5–10, 10–15, or >15 years), taking never users as reference group.<sup>10,23,31</sup> Results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was checked by plotting the  $\log(-\log(\text{survival}))$  vs.  $\log(\text{survival time})$  (Supporting Information, *Figure S1*) and by using Schoenfeld residuals ( $\chi^2 = 21.65$ ,  $P = 0.06$ ). We did not find evidence suggesting potential violation for these results.

Furthermore, Kaplan–Meier curves were used to describe cumulative risk of HF among OC users and non-users. To eliminate the potential confounding effects from the baseline differences, we further performed Kaplan–Meier estimates adjusted for IPTW.

To confirm the robustness of our results, we conducted a series of sensitivity analyses by (i) excluding women ever using HRT; (ii) excluding women with history of breast cancer; (iii) excluding women with history of hysterectomy or oophorectomy; (iv) restricting analysis to post-menopausal women; and (v) using multiple imputation method. In this method, missing values on baseline covariates were imputed using Markov chain Monte Carlo multiple imputation method before their inclusion in the full adjusted models. Finally, results from 10 multiple imputation cycles were combined together to draw a final output.

In the secondary analysis, we used linear regression model to evaluate the relation of OC use to individual cardiac parameter. Because cardiac structure was influenced by age, race, and history of hypertension and diabetes,<sup>32</sup> we adjusted the above covariates in our model.

All data were analysed using STATA Version 15.1 (StataCorp/SE, College Station, TX). All statistical tests were two sided, and the significance level was set at 0.05.

## Results

### Study population

*Figure 1* exhibited the flow chart of the studied population. After excluding male and female participants with unavailable data on OC use, the primary analysis comprised a total of 3594 women. The average age was 62.10 (10.24) years, and 1360 (37.84%) were self-identified as White. As presented in *Table 1*, participants taking OCs were younger, more often smokers and drinkers, with higher education

levels, and had lower proportion of hypertension, diabetes, history of breast cancer, and history of hysterectomy or oophorectomy. Additionally, OC users tended to have more favourable cardiovascular risk profiles, including a lower level of fasting serum glucose, low-density lipoprotein cholesterol, total cholesterol, triglycerides, and higher HDLC level. Other baseline demographics and clinical characteristics by OC use are also shown in *Table 1*.

### Oral contraceptive use and risk of heart failure

A total of 138 incident HF occurred during an average follow-up of 12.45 (3.75) years (44, 562 person-years), among which 105 were definite HF. In unadjusted Cox proportional hazards model, OC use was associated with a decreased risk of HF (HR = 0.45, 95% CI 0.31–0.64,  $P < 0.001$ ). In the age-adjusted and multivariable-adjusted models, the results were attenuated and became non-significant (HR = 0.88, 95% CI 0.59–1.32,  $P = 0.53$  and HR = 0.96, 95% CI 0.63–1.48,  $P = 0.86$ , respectively). Because the baseline characteristics were imbalanced, we further used the IPTW approach to assess the associated risks. After IPTW, all weighted baseline characteristics were well balanced between the two groups, with the vast majority of ASD less than 10% (Supporting Information, *Table S1* and *Figure S2*). Similarly, in the IPTW and adjusted IPTW models, we found no significant association between OC use and HF risk (HR = 0.79, 95% CI 0.45–1.40,  $P = 0.43$  and HR = 0.64, 95% CI 0.33–1.23,  $P = 0.18$ , respectively). When using definite HF as the outcome or stratifying HF into HF with preserved ejection fraction and HF with reduced ejection fraction, identical patterns of association were observed (*Table 2*).

We also assessed the risk of HF with duration of OC use. As demonstrated in *Table 3*, duration of OC use was not related to increased risks of incident HF in the adjusted models, as either a continuous or categorical variable. Likewise, in the sensitivity analyses, non-significant associations of HF and HF subtypes with OC use were found in the multivariable-adjusted models (Supporting Information, *Table S2*).

### Oral contraceptive use and Kaplan–Meier estimates for heart failure

*Figure 2* illustrates the Kaplan–Meier estimates for cumulative risks of incident HF among OC users and non-users. In the crude estimates, compared with non-users, the use of OCs was associated with a significantly lower risk of incident HF. However, when adjusted for IPTW, the weighted cumulative risks were identical between the two groups.

**Table 1** Baseline characteristics of the studied participants by use of oral contraceptives

	Total (n = 3594)	Never user (n = 1850)	Ever user (n = 1744)	P value
Age (years)	62.10 (10.24)	66.51 (9.98)	57.43 (8.25)	<0.001
Body mass index (kg/m <sup>2</sup> )	28.76 (6.17)	28.38 (5.99)	29.16 (6.35)	<0.001
Systolic blood pressure (mmHg)	127.06 (23.19)	131.56 (23.78)	122.28 (21.55)	<0.001
Diastolic blood pressure (mmHg)	69.11 (10.16)	69.09 (9.98)	69.13 (10.35)	0.90
Smoking status				<0.001
Never smoker	2117 (59.10%)	1224 (66.49%)	893 (51.29%)	
Former smoker	1047 (29.23%)	462 (25.10%)	585 (33.60%)	
Current smoker	418 (11.67%)	155 (8.42%)	263 (15.11%)	
Smoking (pack-years)	8.15 (17.04)	6.94 (15.71)	9.45 (18.27)	<0.001
Race				<0.001
White	1360 (37.84%)	608 (32.86%)	752 (43.12%)	
Non-White	2234 (62.16%)	1242 (67.14%)	992 (56.88%)	
Alcohol use				<0.001
Never drinker	1065 (29.88%)	727 (39.73%)	338 (19.49%)	
Former drinker	761 (21.35%)	372 (20.33%)	389 (22.43%)	
Current drinker	1738 (48.77%)	731 (39.95%)	1007 (58.07%)	
Marital status				<0.001
Married or in domestic partnership	1809 (51.03%)	834 (45.67%)	975 (56.72%)	
Widowed	706 (19.92%)	522 (28.59%)	184 (10.70%)	
Separated or divorced	1030 (29.06%)	470 (25.74%)	560 (32.58%)	
Education level				<0.001
Elementary school only	431 (12.03%)	317 (17.22%)	114 (6.55%)	
High school only	1015 (28.34%)	606 (32.92%)	409 (23.49%)	
Some college or technical school	1063 (29.68%)	485 (26.34%)	578 (33.20%)	
College and above	1073 (29.96%)	433 (23.52%)	640 (36.76%)	
History				
Breast cancer	91 (2.53%)	54 (2.92%)	37 (2.12%)	0.13
Hysterectomy	1257 (34.98%)	689 (37.26%)	568 (32.57%)	0.005
Oophorectomy	866 (24.10%)	479 (25.89%)	387 (22.19%)	0.002
Hypertension	1677 (46.66%)	1002 (54.16%)	675 (38.70%)	<0.001
Diabetes mellitus	410 (11.45%)	258 (13.95%)	152 (8.78%)	<0.001
Ever pregnant	3141 (87.44%)	1597 (86.37%)	1544 (88.58%)	0.07
Age at first birth (years)	23.32 (5.11)	23.27 (4.98)	23.38 (5.26)	0.59
Fasting glucose (mg/dL)	94.84 (27.49)	97.34 (28.12)	92.17 (26.55)	<0.001
Low-density lipoprotein cholesterol (mg/dL)	117.69 (31.87)	118.75 (31.91)	116.58 (31.80)	0.04
High-density lipoprotein cholesterol (mg/dL)	56.24 (15.27)	55.62 (15.00)	56.90 (15.52)	0.01
Total cholesterol (mg/dL)	199.57 (35.61)	200.87 (35.32)	198.18 (35.86)	0.02
Triglycerides (mg/dL)	128.27 (82.37)	133.04 (82.65)	123.19 (81.80)	<0.001

## Oral contraceptive use and secondary outcomes

Table 4 summarizes the HRs and 95% CI of the secondary outcomes with OC use. Similar to the outcome of HF, OC use seems to be protective for all-cause death, total CVDs, MI, and stroke in the unadjusted model. However, this association disappeared and became non-significant after adjusting for sociodemographic and cardiovascular risk factors.

## Oral contraceptive use and cardiac structure

To further evaluate the effect of OC use on cardiac structure, we assessed a subset of participants with MRI information on cardiac structure. As presented in Supporting Information, Table S3, OC users had significantly higher stroke volumes and greater ventricular mass for both sides. However, when corrected by body surface area, the LV mass index of OC users became smaller than non-users. Likewise, in regression models adjusted for age, race, and history of hypertension or

diabetes, the use of OCs was positively associated with LV stroke volume [coefficient ( $\beta$ ) = 1.76,  $P$  = 0.01], right ventricular stroke volume ( $\beta$  = 2.17,  $P$  = 0.005), and LVEDM ( $\beta$  = 3.04,  $P$  = 0.006) but had no impact on LVEF ( $\beta$  = 0.09,  $P$  = 0.75), right ventricular ejection fraction ( $\beta$  = 0.33,  $P$  = 0.25), tricuspid annular plane systolic excursion ( $\beta$  = -0.04,  $P$  = 0.92), and RVEDM ( $\beta$  = 0.08,  $P$  = 0.64).

## Discussion

### Main findings

Overall, our study demonstrated that OC use was positively associated with stroke volume and ventricular mass but had no impact on cardiac function. More importantly, in this 12 year prospective cohort study, with 44 562 person-years of follow-up, ever use of OCs had no material increase in their

**Table 2** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident heart failure (HF) and HF subtypes with use of oral contraceptives

	Non-adjusted model		Age-adjusted model		Multivariable-adjusted model		IPTW model		Adjusted IPTW model	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Total incident HF	0.45 (0.31–0.64)	<0.001	0.88 (0.59–1.32)	0.53	0.96 (0.63–1.48)	0.86	0.79 (0.45–1.40)	0.43	0.64 (0.33–1.23)	0.18
Definite HF	0.40 (0.26–0.61)	<0.001	0.76 (0.47–1.21)	0.25	0.80 (0.48–1.31)	0.37	0.65 (0.33–1.27)	0.21	0.56 (0.26–1.21)	0.14
Incident HFpEF	0.54 (0.31–0.95)	0.03	0.96 (0.51–1.81)	0.9	1.07 (0.55–2.08)	0.84	0.76 (0.32–1.81)	0.54	0.58 (0.23–1.49)	0.26
Incident HFpEF	0.39 (0.23–0.67)	0.001	0.79 (0.44–1.45)	0.45	0.87 (0.45–1.68)	0.68	0.75 (0.32–1.78)	0.51	0.65 (0.25–1.71)	0.38

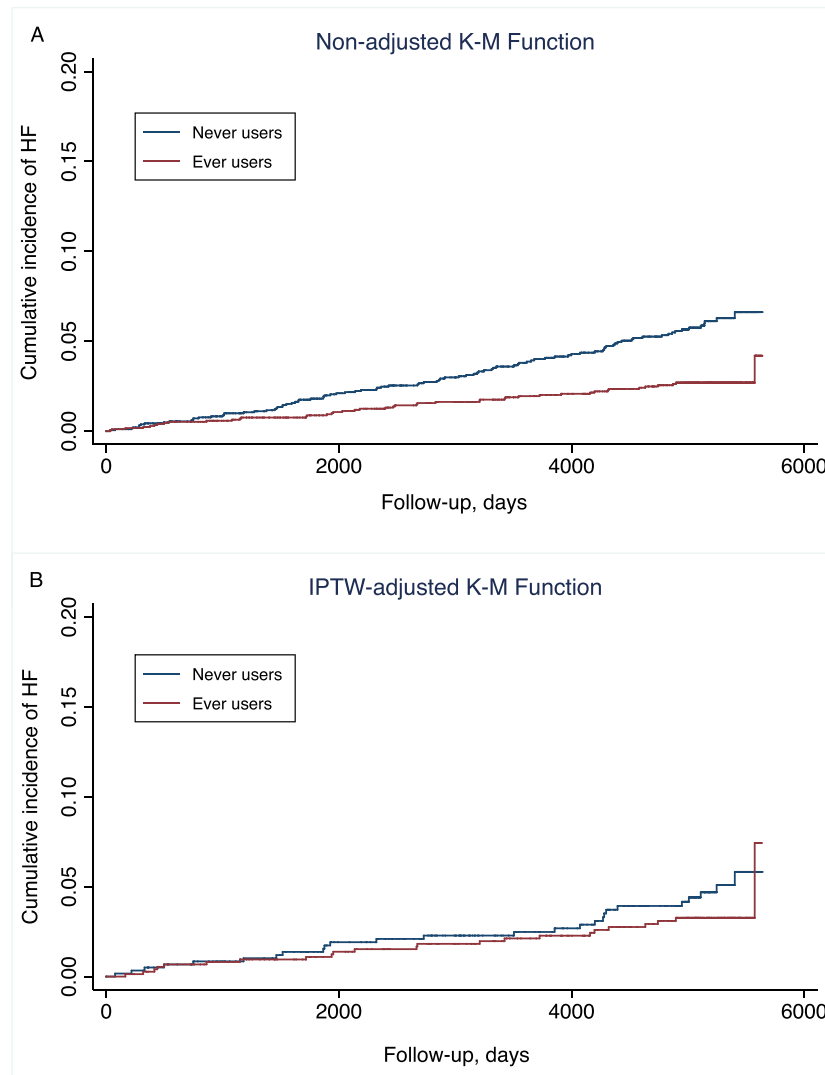
HFpEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; IPTW, inverse probability of treatment weighting. Multivariable-adjusted model: model adjusted for age, race, smoking status, education level, ever use of hormone replacement therapy, drinking status, history of hypertension and diabetes, body mass index, and fasting serum glucose and lipid profiles. IPTW model: model adjusted for IPTW. Adjusted IPTW model: a combination of IPTW and covariate adjustment correcting for residual imbalances after weighting, including age at first birth, race, history of breast cancer, and high-density lipoprotein cholesterol.

**Table 3** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident heart failure with duration of oral contraceptive use

	Non-adjusted model		Age-adjusted model		Multivariable-adjusted model		IPTW model		Adjusted IPTW model	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
<i>Continuous</i>										
Duration (years)	0.91 (0.86–0.96)	<0.001	0.96 (0.92–1.01)	0.08	0.95 (0.90–1.01)	0.13	0.96 (0.91–1.02)	0.17	0.99 (0.93–1.04)	0.63
<i>Categorical</i>										
Never users	1.0		1.0		1.0		1.0		1.0	
0–5 years	0.62 (0.39–0.97)	0.04	1.16 (0.71–1.88)	0.56	1.25 (0.75–2.10)	0.39	1.02 (0.51–2.04)	0.47	0.92 (0.43–1.99)	0.59
5–10 years	0.36 (0.17–0.76)	0.008	0.70 (0.32–1.55)	0.38	0.77 (0.35–1.72)	0.53	0.75 (0.26–2.14)	0.26	0.60 (0.18–1.99)	0.41
10–15 years	0.26 (0.09–0.70)	0.008	0.49 (0.18–1.36)	0.17	0.56 (0.20–1.57)	0.27	0.27 (0.04–1.97)	0.43	0.29 (0.04–2.17)	0.86
> 15 years	0.34 (0.13–0.94)	0.04	0.60 (0.22–1.64)	0.32	0.67 (0.24–1.86)	0.44	1.37 (0.48–3.89)	0.36	1.34 (0.40–4.46)	0.18

Multivariable-adjusted model: model adjusted for age, race, smoking status, education level, ever use of hormone replacement therapy, drinking status, history of hypertension and diabetes, body mass index, and fasting serum glucose and lipid profiles. IPTW model: model adjusted for inverse probability of treatment weighting (IPTW). Adjusted IPTW model: a combination of IPTW and covariate adjustment correcting for residual imbalances after weighting, including age at first birth, race, history of breast cancer, and high-density lipoprotein cholesterol.

**Figure 2** Cumulative incidence of incident heart failure (HF) between oral contraceptive users and non-users. The upper panel (A) shows a lower risk of HF in oral contraceptive users in the crude Kaplan–Meier estimates. The lower panel (B) is the Kaplan–Meier estimates adjusted for inverse probability of treatment weighting (IPTW).



risk of incident HF, all-cause death, total CVDs, MI, and stroke, as compared with women who had never used.

### Oral contraceptive use and cardiovascular health

Oral contraceptives are the most popular method of contraception worldwide, with more than 80% of sexually active fertile women reporting their use.<sup>33,34</sup> However, some safety concerns of OC use on cardiovascular system, including an increased incidence of hypertension, venous thromboembolism, stroke, and MI, have been reported.<sup>7–10,17,18,21</sup> In a meta-analysis published in 2015, the risk of MI or ischaemic stroke was 1.6-fold increase in women using OCs.<sup>35</sup> While in several other studies, OC use was associated with ischaemic

stroke but not MI.<sup>8,10,36</sup> This is in part in concert with what we found in this study. From the present analysis, there was a non-significant trend for OC use to be associated with higher stroke risk. However, we did not observe an increased risk of total CVDs, MI, and all-cause death with OC use. The disparity of this association could be possibly ascribed to the following reasons: current use or former use of OCs, the preparations or formulations of OCs, and baseline medical morbidities of the enrolled population. In an analysis from the Nurses' Health Study, past users of OCs had no increased risk of CVDs.<sup>19</sup> Likewise, in the study reported by Gillum *et al.*, stroke risk was associated with current OC use but not with past use.<sup>17</sup> This suggests that the use of OCs increases the risk of CVDs primarily by altering more acute process, particularly by predisposing to hypercoagulation and

**Table 4** Hazard ratios (HRs) and 95% confidence intervals (CIs) of the secondary outcomes with oral contraceptive use

	All-cause death		Total CVD		Myocardial infarction		Stroke	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Non-adjusted model	0.40 (0.33–0.48)	<0.001	0.55 (0.45–0.68)	<0.001	0.51 (0.34–0.75)	0.001	0.56 (0.39–0.78)	0.001
Age-adjusted model	0.99 (0.81–1.22)	0.93	1.02 (0.81–1.29)	0.87	0.83 (0.54–1.29)	0.41	1.12 (0.76–1.65)	0.57
Multivariable-adjusted model	1.01 (0.81–1.26)	0.91	1.06 (0.82–1.36)	0.68	0.91 (0.57–1.47)	0.70	1.22 (0.80–1.85)	0.35
IPTW model	0.81 (0.60–1.09)	0.17	0.93 (0.67–1.30)	0.68	0.81 (0.46–1.44)	0.48	1.06 (0.59–1.91)	0.84
Adjusted IPTW model	0.71 (0.51–0.99)	0.04	0.85 (0.59–1.22)	0.37	0.57 (0.30–1.09)	0.09	1.07 (0.57–2.00)	0.84

CVD, cardiovascular disease; IPTW, inverse probability of treatment weighting.

Multivariable-adjusted model: model adjusted for age, race, smoking status, education level, ever use of hormone replacement therapy, drinking status, history of hypertension and diabetes, body mass index, and fasting serum glucose and lipid profiles. IPTW model: model adjusted for IPTW. Adjusted IPTW model: a combination of IPTW and covariate adjustment correcting for residual imbalances after weighting, including age at first birth, race, history of breast cancer, and high-density lipoprotein cholesterol.

thrombo-embolism.<sup>7,19,37</sup> Further, baseline medical conditions, like hypertension, obesity, and dyslipidaemia, might portend a higher risk of thrombosis in women ingesting OCs.<sup>36,38–40</sup> On the other hand, the various preparations or formulations of OCs reported in different studies could also be the source of inconsistency. In a recent umbrella review on reproductive health and CVDs, current use of combined contraceptives (oestrogen and progesterone) was associated with 1.5-fold to 19-fold increase risk of ischaemic heart disease, while no association was found between CVDs and current use of progesterone-only contraceptives.<sup>40</sup> It is being believed that newer-generation preparations of OCs tend to be associated with less elevated risk.<sup>9,17</sup> Women using an OC with 20 µg of oestrogen had a lower risk than using an OC with 30–40 µg of oestrogen.<sup>18</sup> Therefore, when designing studies on OCs, the earlier factors should be particularly considered.

### Oral contraceptive use and heart failure risk

Despite the thorough discussion on OC use and CVDs, we were unable to find any studies relating the use of OCs to the occurrence of HF. Although analysis in a report from the Women’s Health Initiative study suggested numerous reproductive factors were associated with increased risk of HF, the effect of OC use was not examined.<sup>41</sup> Therefore, we first reported the association of OC use and incident HF, which extends the findings on the safety of OC use and cardiovascular health. Similar to the earlier outcomes, we found no overall increase in risk of HF with OC use. Although OC use seems to relate to a lower risk of HF in non-adjusted models, this association was attenuated and became non-significant after different degrees of adjustment. This indicates that the beneficial effect of OCs on HF was confounded by some other covariates. As presented in *Table 1*, OC users tended to be younger and have a better cardiovascular risk profile, which could be the reason why a lower HF risk was observed. On the other hand, when examining the results by duration of use, non-significant associations were also documented. If OCs play a role in the development of HF, one would expect that long-term use would pose greater risk than short-term use, and the results should be presented in a dose-responsive manner.<sup>19</sup> However, our data do not support this hypothesis, which suggests that the null findings are internally consistent and unlikely to be observed by chance.

### Oral contraceptive use and cardiac structure

Despite the widespread attention of OC use to CVDs, little is known about their impacts on ventricular size and function.<sup>21,42</sup> It has been suggested that oestrogen replacement limits transverse aortic constriction-induced myocyte



hypertrophy and preserves LV systolic function and contractility.<sup>43</sup> Furthermore, in a genetic mouse model of chronic HF, oestrogen improves cardiac contractility and prevents progressive cardiac enlargement by activating thioredoxin reductase, inhibiting nicotinamide adenine dinucleotide phosphate oxidase activity, and reducing oxidative stress in the heart.<sup>44</sup> However, in our secondary analysis, we did not find such a significant association between OC use and cardiac function, of either the left or right ventricle. Conversely, we observed a positive relationship of OC use and ventricular mass and stroke volume, which was identical to the findings from a previous invasive study.<sup>42</sup> This observation may be due in part to the fluid-retaining and growth-promoting effects of oestrogen.<sup>45,46</sup> However, this did not cause an increased risk of HF, and further investigation should be warranted.

### Strengths and limitations

The major strengths of our study include the prospective design with a long follow-up duration, the adjudication of HF and HF subtypes, the ability to analyse the effect of OCs on cardiac parameters and account for multiple potential confounders using different degrees of adjustment models, and conducting a series of sensitivity analyses, which largely reduce the inherent bias of observational study. Importantly, because a prospective double-blind study of OCs in women of reproductive age is infeasible, our findings provide important insights into the safety of OC use and cardiovascular health.

However, limitations should be acknowledged. First, although multivariable and IPTW adjustments were extensively applied in this study, we cannot exclude the possibility of additional unmeasured residual confounders. Second, reproductive data were self-reported and subject to reporting bias. In addition, information was not sought on the brand or type of OC used, which precluded our detailed investigation on the effect of certain types of OCs. Further studies are needed to determine whether the effect of OCs varied across different dosages and formulations. Third, although we found non-significant reduced risk of HF with the use of OCs, there is a chance that the null results were attributed to the limited number of HF events. However, similar findings observed in secondary outcomes further suggest the safety of OC use. Finally, our sample consisted of US women free of baseline CVDs, which limits the generalizability of our results to other ethnicities or women with pre-existing CVDs.

### Conclusions

Given the popularity of OC use and their potential consequences on cardiovascular system, examining the association

between HF and OC use is of paramount importance. In this study, we found for the first time that OC use was correlated with a higher stroke volume and greater ventricular mass but did not portend an increased risk of HF, regardless of the duration of use. However, whether the formulations or dosages differently impact this relationship should be further investigated.

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### Conflict of interest

None declared.

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### Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Baseline characteristics of oral contraceptives users and non-users after inverse probability of treatment weighting (IPTW).

**Table S2.** Hazard ratios (HR) and 95% confidence intervals (95%CI) of incident heart failure (HF) and HF subtypes with use of oral contraceptives across a series of sensitivity analysis using multivariable-adjusted models.

**Table S3.** Comparison of cardiac structural parameters between oral contraceptive (OC) users and non-users.

**Figure S1.** The log(−log (survival)) versus log (survival time) plots. No violation was found in the proportional hazards assumption.

**Figure S2.** Standardized mean biases comparing the full unmatched cohort with the inverse probability of treatment weighting (IPTW) matched cohort. SBP = systolic blood pressure.

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