Original Article

12-Year Follow-Up Study of the C-Reactive Protein in Iranian Middle-Aged Women: Isfahan Cohort Study

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Abstract

Background: As an important inflammatory marker, study of C-reactive protein (CRP) changes over time may lead to better identification of risk factors of cardiovascular disease. We evaluated the relationship between CRP changes and lifestyle, metabolic syndrome (MS) and body mass index (BMI) in middle-aged women and explored potential bias from attrition. **Materials and Methods:** We studied 1234 participants in the Isfahan cohort study – a longitudinal population-based study of adults older than 35 years living in urban and rural areas of three counties in central Iran. Data were collected every 6 years since 2001 (3 points). Random effects model was used to evaluate the effects of behavioural risk factors and MS on CRP, with pattern mixture model to account for cohort attrition. **Results:** Mean CRP levels decreased over time (Est = −0.066, $P < 0.001$). MS (Est = −0.195, $P < 0.001$), BMI (Est = 0.022, $P < 0.001$), physical activity (Est = −0.009, $P = 0.002$) and history of smoking (Est = −0.399, $P = 0.002$) were independently associated with increases in CRP. Pattern mixture model showed that CRP decreased in participants with monotone measurement (Est = −0.032, $P < 0.001$), as well as intermittent measurement (Est = −0.022, $P < 0.001$), with no association in participants who responded at all points (Est = −0.015, $P = 0.083$). **Conclusion:** In this study, the rate of changes in CRP level in middle-aged women over time was higher in participants who were irregularly measured than those who measured continuously. MS, BMI and physical activity may be related to the CRP changes over time in middle-aged women.

Keywords: C-reactive protein, metabolic syndrome, middle-aged women, missing data, pattern mixture model

Introduction

C-reactive protein (CRP) is an acute phase reactant, produced by the liver. Elevated level of CRP, as an inflammatory biomarker, can be identified with blood tests within a few hours after tissue injury or other cause of inflammation. Inflammation of the arteries is a risk factor for cardiovascular disease.[1] It has been associated to an increased risk of arterial disease, heart attack, heart disease and stroke.[2] Even without any symptoms of disease, a high level of CRP may independently suggest an increased risk for nearly all degenerative disorders, including cancer, cardiovascular disease and diabetes.[3] The chronic inflammation behind an elevated level of CRP may be influenced by inappropriate dietary patterns, lack of physical activity, smoking, genetics and environmental factors.[4] In addition, CRP levels have also been reported to differ by gender.[5] Existing evidence also proposed that CRP level might be more strongly correlated with metabolic syndrome (MS) in women than in men.[6]

As women age and undergo menopause, they may experience a wide range of chronic diseases such as cardiovascular diseases. The reasons for the high prevalence of health-related problems in middle-aged women are multifactorial,[7] and more studies can improve their quality of life in the old age. In a cross-sectional study, McDade *et al*.[8] showed that waist circumference was the strongest anthropometric predictor of elevated CRP in Filipino women.

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Several cross-sectional studies have demonstrated significant associations between CRP levels and other risk factors for cardiovascular diseases such as blood pressure, triglyceride levels, high-density lipoprotein cholesterol levels, low-density lipoprotein and total cholesterol.[9-12] However, there is little information to understand the relationship between longitudinal changes in CRP and other risk factors of cardiovascular disease, with genetic, environmental factors or lifestyle interventions. A longitudinal study conducted by Camhi *et al*.[13] to assessing the effect of lifestyle intervention on CRP showed a significant decrease in CRP levels among women with MS, but not in men. However, Heilbronn *et al*.[14] did not find a significant association between CRP levels with change in lipids or glucose in response to a low-fat diet weight loss program.

Although a longitudinal study may provide a relevant picture of patients' follow up, however, one of the issues with these studies is missing data. Participants experiencing deteriorating health because of progressive disease are more likely to discontinue the follow-up. As a result, more data are missing in these participants compared with those who continue the follow-up and lead to participants with various response patterns. A commonly used approach is analysis based on completers (who complete the follow-up survey) only and exclude the participants with missing data from the final analysis. However, often, the probability of missingness on a variable is related to the values of that variable itself, even after controlling for other variables. In this situation, the missing measurement itself is informative, and estimates obtained from complete case analysis may be biased.[15] To address this, two different approaches to analysis of longitudinal data were introduced by Little and Rubin (1993, 1994): selection modelling and pattern mixture model (PMM).[16] Recently, pattern mixture models have reached considerable interest due to some dominant features.[7,17] Pattern mixture models can be applied to evaluate the contribution of missingness to the outcome variable by including missing data patterns as a predictor in model.

To assess the changes in CRP level over 12-year follow-up in Iranian middle-aged women and to test the association between behavioural risk factors of cardiovascular disease and MS with CRP changes, we present a linear mixed effect model (LMEM) and a PMM with multiple imputation approach as sensitivity analysis to check whether various response patterns lead to different results or not.

Materials and Methods

Participants and measurements

Participants were women aged 35–60 years participating in the Isfahan cohort study (ICS) – a longitudinal population-based study of adults aged 35 years old or more, living in urban and rural areas of three counties in central Iran. The ICS has been started since 17 years ago (2001) as a part of baseline study of Isfahan Healthy Heart Program, and each of the participants was followed every 6 years. All participants gave their informed consent for inclusion before they participated in the study. Ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Centre, a World Health Organization collaborating centre. All participants were assessed for demographic characteristics, medical history, related lifestyle behaviours (including smoking, physical activity and dietary behaviour) and other risk factors. Smoking status (current smokers/nonsmokers), physical activity (mean hours per week) and dietary behaviour (according to the Global Dietary Index[18]) were determined by self-report. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).[19]

The primary objective of this study was to determine the relationship between changes in CRP levels with BMI, MS and lifestyle behaviours including smoking, physical activity and nutritional habits in middle-aged women over the 12-year study time frame. CRP was measured using the immunoturbidimetry method with autoanalyser (Hitachi 902) with Pars Azmun kit (Iran). MS was calculated using adult treatment panel (ATP III) criteria[20] over an average follow-up of 12 years. According to ATP III criteria, MS is defined as having at least three of the five criteria: (1) waist circumference >102 cm in men and >88 cm in women, (2) serum triglyceride >150 mg/dl, (3) high-density lipoprotein <40 mg/dl in men and <50 mg/dl in women, (4) fasting blood sugar >110 mg/dl and (5) blood pressure >130/85 mmHg.

All variables were measured at baseline in 2001 and at 6 and 12 years of follow-up. However, CRP test for some of the participants was missed on one or more measurement times. Information on CRP measurement was not fully recorded, and only if needed, this test was conducted. Hence, it is thought that patients with a worse health status were more likely to be measured for CRP. Accordingly, we classified participants into three groups based on the order of CRP measurements: continuous measurement (who measured at all times due to a worse health status), intermittent measurement (who did not have a stable health status) and monotone measurement (who first had a bad health status but then got better) [Table 1].

We evaluated whether different patterns of missing data were associated with different relationships between CRP and behavioural risk factors of cardiovascular disease and MS.

Table 1: Pattern of the participant's C-reactive protein measurements in Isfahan cohort study

Pattern of CRP measurement	2001 (baseline)	2007 (6 year)	2013 (12 year)
Continuous	✓	✓	✓
Intermittent	✓	×	✓
	×	×	✓
	×	✓	✓
	×	✓	×
Monotone	✓	×	×
	✓	✓	×

CRP: C-reactive protein

Statistical analysis

We applied a LMEM with variance components' covariance structure for analysing the CRP levels, with time, BMI, MS, physical activity (activity), dietary behaviour (diet) and history of smoking (smoke) as fixed effects and individual subject as random effect. Because the distribution of CRP levels is asymmetric, the natural logarithm of CRP was used as the dependent variable. In this study, many CRP measurements contained missing values. The LMEM assumes that the missing data are missing at random meaning that the mechanism of the missingness is independent of the unobserved values. If the missingness is informative (if missingness is related to patient health status), then analysis may be biased. A PMM with multiple imputation approach was also used to analyse the CRP as sensitivity analyses, to adjust for bias that may potentially occur by patient attrition. Under this approach, different patterns of missing data are identified to explicitly model the missing data distribution.[21,22]

First, the missing data in intermittent and monotone patterns were imputed in multiple versions, assuming that dropouts are missing not at random. Then, imputed data were pooled with completers and a LMEM was fitted again. Mean changes from baseline were estimated and compared between different patterns. The LMEM and PMM were fitted in R software (version 3.3.3, The R Foundation for Statistical Computing,. Vienna, Austria) using the lme4 and mice packages. $P < 0.05$ was considered as statistically significant.

Results

In ICS, the overall percentage of missing observations for CRP was 24.6%. Only 27.5% of participants had available CRP data at all three waves (continuous measurement). The most common missing data pattern was intermittent (43.8%), and 28.7% were monotone.

Of 1234 participants included in the study, 238 (19.3%) had MS at baseline, increasing to 51.9% at 12 years. Mean CRP increased during the 1st 6-year period (1.84 ± 0.51) and then decreased during the 2nd 6-year period (2.12 ± 0.14). The total changes from the baseline in CRP level were 0.28 ± 0.65. More details on descriptive statistics of the study participants are presented in Table 2 for each time point.

The estimated mean CRP level changes from baseline through 12 years with and without regard to the measurement patterns are shown in Figure 1. All measurement patterns showed a trend consistent with changes in CRP level in all individuals without imputation. Participants with continuous measurements were consistently lower than the other groups over the first 6 year.

The results from LMEM and PMM are displayed in Table 3. Findings from the LMEM analysis suggest that, except for dietary habits, all other predictors were independently associated with either positive or negative changes in CRP. Mean change from baseline in CRP level indicated significant decrease (−0.066, $P < 0.001$). An increase in physical activity was independently associated with decrease in CRP changes. Middle-aged women without MS had more decrease in CRP than those with MS (−0.195, $P < 0.001$). Furthermore,

Table 2: Study participant characteristics at each time point

Variables	Baseline	6 year	12 year
CRP (mean±SD)	3.01±2.89	4.85±3.40	2.73±3.54
BMI (mean±SD)	28.15±4.82	28.89±4.60	28.92±4.62
Activity (mean±SD)	12.09±7.16	12.18±6.49	11.85±5.89
Diet (mean±SD)	1.12±0.23	0.94±0.27	0.98±0.28
MS, *n* (%)			
Yes	238 (19.3)	564 (45.7)	640 (51.9)
No	996 (80.7)	670 (54.3)	594 (48.1)
Smoke, *n* (%)			
Yes	33 (2.7)	30 (2.4)	31 (2.5)
No	1201 (97.3)	1204 (97.6)	1203 (97.5)

CRP: C-reactive protein, BMI: Body mass index, Activity: Physical activity, Diet: Dietary behaviour, MS: Metabolic syndrome, SD: Standard deviation

Table 3: Model estimates and standard error for random effects model and pattern mixture model

Variables	LMEM		PMM	
	Est (SD)	*P*	Est (SD)	*P*
Intercept	1.475 (021)	<0.001	1.127 (0.254)	0.001
Time	−0.066 (0.005)	<0.001	−0.027 (0.008)	0.018
MS (reference=yes)	−0.195 (0.04)	<0.001	−0.104 (0.047)	0.046
BMI	0.022 (0.004)	<0.001	0.025 (0.004)	<0.001
Activity	−0.009 (0.003)	0.002	−0.009 (0.003)	<0.001
Diet	0.115 (0.06)	0.078	−0.157 (0.084)	0.087
Smoke (reference=yes)	−0.399 (0.13)	0.002	−0.435 (0.191)	0.055

BMI: Body mass index, Activity: Physical activity, Diet: Dietary behaviour, MS: Metabolic syndrome, SD: Standard deviation, LMEM: Linear mixed effect model, PMM: Pattern mixture model

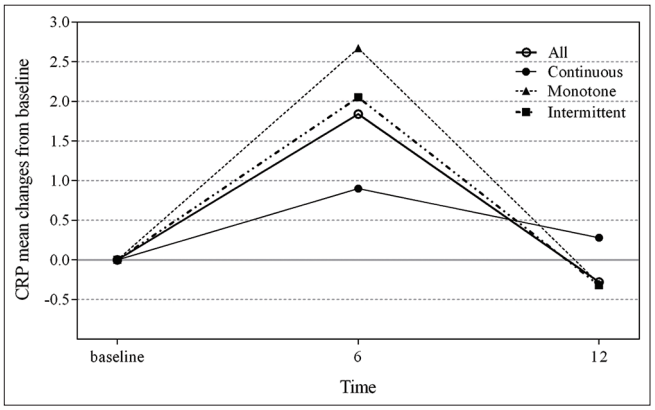

Figure 1: Estimated mean C-reactive protein changes from baseline over time. All, all participants regardless of the pattern of C-reactive protein measurement and without imputation. Continuous, who have been measured for C-reactive protein at all time. Monotone, participants with monotone measurement pattern and with imputation. Intermittent, participants with monotone measurement pattern and with imputation.

compared to the nonsmoker, participants with a history of smoking have experienced more increase in CRP by 0.399 points ($P = 0.002$).

After missing data imputation, random effect PMM has revealed the same outcomes. Imputed measurements had less decrease in CRP than unimputed measurements over time (−0.027, $P = 0.018$). In contrast, the relationship between dietary and history of smoking was not associated with CRP level changes.

Results from the LMEM for each of the patterns separately are summarised in Table 4. For continuous measurement, only BMI and dietary habit were significantly associated with change in CRP. One unit increase in BMI is associated with a 0.046 unit increase in mean changes of the natural logarithm of CRP. However, there was an inverse association between CRP level and dietary habits (−0.394, $P = 0.025$), which signifies that increase in global dietary index (GDI) score (higher GDI shows worse dietary habits) leads to decrease in CRP changes.

For participants who were in monotone pattern, the effect of BMI on CRP level changes was less than continuous pattern (0.018, $P = 0.026$). Compared to the continuous measurement pattern, the CRP level has changed over time in this group of patients (−0.032, $P < 0.001$).

Under intermittent pattern, which was the most common type of missingness pattern in this study, all predictors were associated with changes in CRP level.

Discussion

In this paper, the pattern mixture approach as a method for correction for informative missingness was studied. In studies with a lot of missing values, it is important to explore whether the missingness is informative or not. We applied this approach on data from ICS to study the longitudinal changes in CRP level among middle-aged women. We focused on lifestyle features, BMI and MS as risk factors of cardiovascular disease. We compared the results of the pattern mixture approach to the results of the commonly used random effects model.

Results of all participants showed that, on average, the CRP level decreased over time. Given the measurement pattern, we found the same results for participants with intermittent measurement, a slight decreasing in CRP level over time for participants with monotone measurement, but no significant association was seen with participants who completed all CRP measurements. The results of the LMEM under intermittent pattern were consistent with the findings of LMEM without imputation because the participants with intermittent measurement were about 75% of the total number of participants.

Under LMEM, we observed a significant difference in CRP between participants with and without MS. However, this relationship was not significant for participants with continuous measurement when LMEM was applied by adjusting on patterns of the participant's CRP measurements. Camhi *et al*. found that plasma CRP levels decreased significantly in response to a diet and a diet plus physical activity intervention in women with MS.[13] In our study, mean change in CRP was greater in participants with MS than in non-MS. Au *et al*. also showed that high CRP levels are associated with MS.[23]

BMI was significantly associated with change in CRP under both approaches. The mean change in CRP was doubled, respectively, from 0.022 and 0.018 in the intermittent and monotone up to 0.046 in the continuous. Data from the National Longitudinal Study of Adolescent Health demonstrated that changes in BMI during the transition from adolescence to adulthood were associated with greater odds of inflammation than current (age 27 years) or past (age 15 years) BMI alone.[24] For schoolchildren, BMI was the most powerful predictor of serum concentrations of CRP. It may be an important factor to control body weight to prevent an increase in serum CRP in children and to help the prevention of chronic diseases.[25] Others have found comparatively stronger associations between BMI gain or loss with CRP increase or decrease than current BMI.[26,27]

Except for participants with intermittent measurement, physical activity was not shown to be a significant predictor of CRP changes. The present study showed that an increase in physical activity may decrease the changes in CRP over time. Sadeghipour *et al*. reported no significant relation between CRP and physical activity.[25] In a longitudinal study, the average

Table 4: Parameter estimates of random effects model by adjusting on patterns of the participant's C-reactive protein measurements

Variables	Continuous		Monotone		Intermittent	
	Est (SD)	*P*	Est (SD)	*P*	Est (SD)	*P*
Intercept	0.425 (0.71)	0.550	0.549 (0.388)	0.158	1.073 (0.19)	<0.001
Time	−0.015 (0.012)	0.083	−0.032 (0.007)	<0.001	−0.022 (0.003)	<0.001
MS (reference=yes)	−0.151 (0.11)	0.165	−0.222 (0.086)	0.011	−0.101 (0.035)	0.005
BMI	0.046 (0.011)	<0.001	0.018 (0.008)	0.026	0.022 (0.01)	<0.001
Activity	0.012 (0.008)	0.152	0.006 (0.006)	0.321	−0.013 (0.003)	<0.001
Diet	−0.394 (0.174)	0.025	0.041 (0.152)	0.789	−0.160 (0.06)	0.012
Smoke (reference=yes)	−0.548 (0.54)	0.312	0.174 (0.211)	0.410	−0.305 (0.11)	0.006

BMI: Body mass index, Activity: Physical activity, Diet: Dietary behaviour, MS: Metabolic syndrome, SD: Standard deviation

changes of CRP were not associated to average current physical activity or to natural changes in current physical activity across the visits.[28]

The association between dietary habits and CRP level was not significant under LMEM as well as PMM. However, this association was different across patterns of measurement. Among participants with continuous or intermittent measurement, a good dietary habits led to a decrease in CRP level, while no association was observed for monotone measurement. Boylan *et al*. observed that the high glycaemic load in dietary habits seems to increase CRP concentrations which, in turn, may lead to increased CVD risk.[29] In a study in Korea, CRP changes related to the food group consumption patterns.[30]

In this study, the results of the PMM with multiple imputations were consistent with the findings of the commonly used random effects model; however, the standard error estimates from PMM tended to be slightly larger for some predictors, implying that the results should be interpreted with caution. Post *et al*. showed that if the standard errors are larger for PMM, then the missing at random assumption within the patterns must be checked by sensitivity analysis.

This study showed that the CRP level in middle-aged women over follow-up time has been decreased. The rate of these changes was more in participants who were irregularly measured for CRP than those who measured at all time, that can be related to their health status. Dietary behaviour and BMI were the only predictors that influenced the CRP changes among participants with continuous measurement. Unlike other participants, changes in CRP over time were stable for participants who were measured at all times.

Conclusion

PMM adjusted the estimates to a certain degree and led to partly different results from the random effects model. Hence, this approach might be considered in the analysis of longitudinal data with large amount of informative missing data.

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Conflicts of interest

There are no conflicts of interest.

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