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Characteristics of apparently healthy individuals with a very low C-reactive protein

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ABSTRACT

Background: The importance of the inflammatory processes and C-reactive protein (CRP) evaluation was observed. Only few studies used cut-off value < 1 mg/L.

We sought to evaluate the association between very low CRP (vlCRP) and health status, to describe the repetition of vlCRP and to identify predictors for repetition.

Methods: A historical cohort study of all participants who underwent a routine annual check-up between January 2002 and July 2018 at the Tel Aviv Sourasky medical center. CRP test was evaluated in all participants. Individuals who use statins or with CRP > 10 mg/L were excluded. CRP ≤ 0.12 mg/L was considered as vlCRP.

Results: The final study cohort included 14,161 individuals. Of them, 5065 were females and mean age was 43.4 years (SD 10.6). vlCRP at first check-up was observed in 1299 (9.2%) of the participants. In multivariable analysis, older age, hyperlipidemia, hypertension and smoking were significantly associated with lower probability of vlCRP. At the second check-up, 50.1% vlCRP repetition was observed with no significant predictor from previous visit.

Conclusion: vlCRP is associated with younger age, non-smoking, and absence of hyperlipidemia and of hypertension. However, it may also be part of the individual physiology.

1. Introduction

C-reactive protein (CRP) is considered as a marker of infection and inflammation. It was suggested to identify patients at intermediate and high risk for cardiovascular events. Individuals with CRP level < 1 mg/L were considered to be at the lower risk group [1,2]. Therefore, it has become a part of the routine patient assessment. A recent study showed that in high risk population, CRP < 2 mg/L is associated with reduced risk for stroke, coronary heart disease and death from coronary heart disease while low density lipoprotein cholesterol < 70 mg/dL was not associated with these outcomes [3]. This finding emphasize the importance of the inflammatory processes.

Today, CRP is measured in individuals who undergo routine health examination [4–13]. While most of the studies based on routine health examination cohorts, used 1 mg/L or higher as the cut-off value, only a few used a lower cut-off values [8–13].

Very low CRP concentration is probably associated with good health as it was suggested that individuals with CRP < 1 mg/L are at low risk for cardiovascular disease. However, it is indistinct if it is associated with good health only, or if it is part of the physiology of the individual.

Therefore, our objectives were to evaluate the association between very low CRP level in patients undergoing routine health examination and health status, to describe the repetition of very low CRP in these patients and to identify predictors for very low CRP repetition.

2. Methods

2.1. Study design and population

A cross sectional and historical cohort study of all participants who

Abbreviations: CRP, C-reactive protein; vlCRP, Very low CRP; wrCRP, Wide range CRP; OR, Odds ratio; CI, Confidence interval; IQR, Interquartile range; GEE, Generalized estimating equation

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Table 1
Participants' characteristics.

Characteristic	*N* = 14,161
Demographic characteristics	
Male, n(%)	9096 (64.2%)
Age (years), median (IQR)	43.1(35.6–51.1)
Smoking status, n(%)	
Current	2333 (16.5%)
Past	3214 (22.8%)
Never	8574 (60.7%)
Morbidity	
Cardiovascular disease, n(%)	266 (1.9%)
Diabetes mellitus, n(%)	300 (2.1%)
Chronic fatigue or fibromyalgia, n(%)	44 (0.3%)
Chronic pain, n(%)	279 (2.0%)
Liver Disease, n(%)	0 (0.0%)
Hyperlipidemia, n(%)	1419 (10.0%)
Hypertension, n(%)	1230 (8.7%)
Inflammatory bowel disease, n(%)	212 (1.5%)
Peripheral vascular disease, n(%)	80 (0.6%)
Chronic lung disease, n(%)	891 (6.3%)
Rheumatic disease, n(%)	721 (5.1%)
Hypothyroidism, n(%)	397 (2.8%)
Blood tests	
Wide range C-reactive protein (mg/L), median (IQR)	1.04 (0.37–2.78)
Hemoglobin (g/dL), mean (SD)	
Female	13.1 (0.97)
Male	15.0 (0.95)
White blood cells count (K/mcL), median (IQR)	6.5 (5.6–7.6)
Neutrophils	
Count (K/mcL), median (IQR)	3.8 (3.2–4.6)
Percent, mean (SD)	58.9 (7.7)
Lymphocytes	
Count (K/mcL), median (IQR)	1.9 (1.6–2.3)
Percent, mean (SD)	30.3 (6.87)
Platelet count (K/mcL), mean (SD)	248.2 (57.8)
Neutrophil-to-lymphocyte ratio, median (IQR)	1.95 (1.57–2.5)
Creatinine (mg/dL), mean (SD)	1.05 (0.16)
Albumin (g/L), mean (SD)	45.2 (2.46)
Lactate dehydrogenase (U/L), mean (SD)	311.3 (54.5)

underwent a routine annual check-up between January 2002 and July 2018 at the Tel Aviv Sourasky medical center, a tertiary referral university affiliated 1500 beds medical center located in the center of Israel. CRP test was included in the routine chemistry panel in all participants.

Participants with CRP level above 10 mg/L were excluded from the study as such values may indicate an active inflammatory process [14]. We also excluded participants who use statins since they may lower the CRP values [15].

In order to find predictors for very low CRP, we compared the characteristics of participants who presented in their first visit very low CRP to participants who presented higher values. In the next step, we looked for predictors for recurrent very low CRP at the next check-up test. Only participants who had very low CRP at their first evaluation were included and their baseline characteristics were compared between those who had very low CRP in their second visit and those who didn't. The last analysis evaluates the CRP level and the rate of very low CRP recurrence at all subsequent CRP tests in participants with very low CRP at first check-up evaluation.

2.2. Data source, measurement and variables

Data was obtained from the Tel Aviv Medical Center Inflammation Survey (TAMCIS), a registered data bank of the Israeli Ministry of Justice [11,16–20]. This database includes individuals who have attended the Tel Aviv Medical Center for a routine annual check-up and were asked to be recruited to the inflammation survey. All participants gave their informed consent for participation according to the local ethics committee (TLV-02-049). Data on age, gender, smoking habits, morbidities, complete blood count, creatinine, albumin and lactate dehydrogenase were extracted from the data bank. We defined the value of 0.12 mg/L, the lowest analytical range of CRP in our laboratory, as very low CRP (vlCRP).

2.3. Laboratory method

Wide-Range C-Reactive Protein (wrCRP) was measured by ADVIA, Siemens Healthcare Diagnostics Inc., Tarrytown, NY 10591–5097 USA. The ADVIA® Chemistry wrCRP method measures CRP in serum and plasma by a latex-enhanced immunoturbidimetric assay.

wrCRP measurements were performed on two ADVIA1650 analyzers until July 2014. On May 2014, both analyzers were upgraded to ADVIA2400. On May 2018, we expended the system's capacity by adding one ADVIA1800 analyzer. The harmonization based on internal QC (Bio rad Immunology control) is done monthly to assure compliance between analyzers. According to the Siemens manifest, the ADVIA1650 wrCRP and ADVIA1800 wrCRP have the same performance. The analytical performance of wrCRP was evaluated in each analyzer according conventional protocol [21]. This protocol utilizes analysis of samples containing small but known concentrations of CRP to assess accuracy and repeatability of low concentration CRP beyond the analytical range. The analytical range of wrCRP according to Siemens Inc. is 0.12 mg/L for ADVIA 1800/1650 and 0.003 mg/L for ADVIA2400. The value of 0.12 mg/L was reassessed in our systems. Pooled serum with CRP concentration (0.09–0.45 mg/L) around the analytical range was

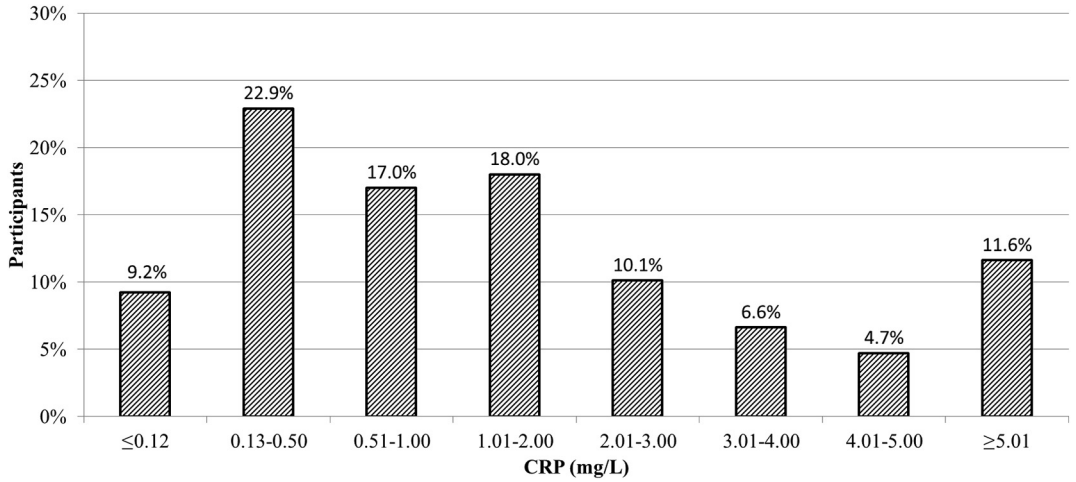

Fig. 1. CRP level at first evaluation.

Table 2
Comparison of participants' characteristics between those with very low CRP (≤0.12 mg/L) and those with higher values.

Characteristic	Wide range C-reactive protein (mg/L)		p
	≤0.12	> 0.12	
	(*n* = 1299)	(n = 12,862)	
Demographic characteristics			
Male, n(%)	807 (62.1%)	8289 (64.4%)	0.096
Age (years), median (IQR)	39.3 (31.5–47.1)	43.5 (36.0–51.5)	< 0.001
Smoking status, n(%)			
Current	194 (15.0%)	2139 (16.7%)	< 0.001
Past	234 (18.1%)	2980 (23.2%)	
Never	864 (66.9%)	7710 (60.1%)	
Morbidity			
Cardiovascular disease, n(%)	21 (1.6%)	245 (1.9%)	0.465
Diabetes mellitus, n(%)	13 (1.0%)	287 (2.2%)	0.003
Chronic fatigue or fibromyalgia, n(%)	5 (0.4%)	39 (0.3%)	0.597
Chronic pain, n(%)	15 (1.2%)	264 (2.1%)	0.026
Hyperlipidemia, n(%)	71 (5.5%)	1348 (10.5%)	< 0.001
Hypertension, n(%)	42 (3.2%)	1188 (9.2%)	< 0.001
Inflammatory bowel disease, n (%)	24 (1.8%)	188 (1.5%)	0.275
Peripheral vascular disease, n (%)	7 (0.5%)	73 (0.6%)	0.895
Chronic lung disease, n(%)	80 (6.2%)	811 (6.3%)	0.835
Rheumatic disease, n(%)	49 (3.8%)	672 (5.2%)	0.023
Hypothyroidism, n(%)	23 (1.8%)	374 (2.9%)	0.018
Blood tests			
Hemoglobin (g/dL), mean (SD)			
Female	13.1 (0.90)	13.1 (0.98)	0.277
Male	14.9 (0.91)	15.0 (0.95)	0.118
White blood cells count (K/mcL), median (IQR)	5.9 (5.1–6.8)	6.6 (5.7–7.7)	< 0.001
Neutrophils			
Count (K/mcL), median (IQR)	3.4 (2.7–4.1)	3.9 (3.2–4.7)	< 0.001
Percent, mean (SD)	57.0 (7.6)	59.1 (7.7)	< 0.001
Lymphocytes			
Count (K/mcL), median (IQR)	1.8 (1.5–2.2)	1.9 (1.6–2.3)	< 0.001
Percent, mean (SD)	31.7 (6.6)	30.2 (6.9)	< 0.001
Platelet count (K/mcL), mean (SD)	233.5 (54.6)	249.7 (57.9)	< 0.001
Neutrophil-to-lymphocyte ratio, median (IQR)	1.84 (1.43–2.29)	2.0 (1.58–2.52)	< 0.001
Creatinine (mg/dL), mean (SD)	1.04 (0.15)	1.05 (0.16)	0.163
Albumin (g/L), mean (SD)	45.5 (2.5)	45.1 (2.5)	< 0.001
Lactate dehydrogenase (U/L), mean (SD)	295.5 (49.4)	312.9 (54.7)	< 0.001

Table 3
Multivariable analysis of determinants to very low CRP (≤0.12 mg/L).

Characteristic	OR (95%CI)[a]	p
Age (years)	0.97 (0.96–0.98)	< 0.001
Male	0.89 (0.79–1.01)	0.057
Smoking status		0.013
Never	1	
Current	0.82 (0.69–0.96)	0.016
Past	0.84 (0.72–0.98)	0.030
Diabetes mellitus	0.74 (0.42–1.31)	0.300
Chronic pain	0.67 (0.38–1.19)	0.170
Hyperlipidemia	0.67 (0.52–0.86)	0.002
Hypertension	0.52 (0.37–0.71)	< 0.001
Rheumatic disease	0.97 (0.72–1.31)	0.821
Hypothyroidism	0.72 (0.47–1.11)	0.135

[a] OR > 1 indicate higher probability for CRP ≤0.12 mg/L and OR < 1 indicate higher probability for CRP > 0.12 mg/L.

prepared separately for ADVIA2400 and for ADVIA1800. This pooled serum divided into aliquots. The aliquots were freezed in -20 °C until the measurement. Measurements were done in duplicate twice a day; the interval between the measurements was 4 h during 10 days. We included various lots and calibrations in order to capture the expected performance of the typical population of analyzers and reagents.

The measurements of wrCRP have a typical normal distribution. The performance of wrCRP measurements in ADVIA 2400 and ADVIA 1800 is presented in Appendix 1.

ADVIA 2400 and ADVIA 1800 had approximate coefficient of variation (%CV): 14.15% and 14.63% in the low concentration of CRP and 5.71% and 6.18%, in the high concentration of CRP, respectively. Decreased in the CRP concentration was associated with increase in %CV (Appendix 2). This association characterized samples with very low concentration. However, wrCRP measurements show a good repeatability and accuracy.

2.4. Statistical analysis

Categorical variables were described using frequency and percentage. Continuous variables were evaluated for normal distribution using histograms and Q-Q plots. Normally distributed continuous variables were described as mean and standard deviation (SD) and non-normally distributed continuous variables were expressed as median and interquartile range (IQR). Chi-Square test was used to compare categorical variables between those who presented very low CRP and those who did not and independent samples *t*-test and Mann-Whitney test were used to compare continuous variables between them. Multivariable logistic regression was used to identify independent predictor for very low CRP. Odd ratio (OR) and 95% confidence interval (CI) were reported. Demographic characteristics and morbidities were included in the multivariable analysis if they were associated with very low CRP at the univariate analysis at a significance level of $p < .2$. Generalized estimating equation (GEE) model was used when all recurrent routine annual check-ups in individuals with vlCRP at first visit were studied. All statistical tests were two tailed. $p < .05$ was considered statistically significant. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 24, IBM Corp., Armonk, NY, USA, 2016) and R (R: A language and environment for statistical computing, version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria, 2017) were used for all statistical analysis.

3. Results

3.1. Participants

Seventeen thousand and one hundred seventy-eight participants visited our routine check-up program during the study period. Of them, 1693 patients used statins, 993 patients had CRP value higher than 10 mg/L at their first visit and in 431 patients, data on statin consumption was not available. The final study cohort included 14,161 individuals. Of them, 5065 (35.8%) were females. The mean age was 43.4 years (SD 10.6). Patients' characteristics are presented in Table 1.

3.2. CRP at first visit

The median CRP level at the first visit was 1.04 mg/L (IQR 0.37–2.78) and 1299 (9.2%) participants had a very low CRP (≤0.12 mg/L). CRP distribution is presented in Fig. 1.

Table 2 presents a comparison between participants with and without very low CRP. Participants with very low CRP were younger, had lower white blood cells, neutrophils and lymphocytes counts, lower platelet count, lower neutrophil to lymphocyte ratio, lower lactate dehydrogenase and higher albumin. Of the current smokers, 8.3% had very low CRP compare to 7.3% of those participants who had smoked in the past and 10.1% of those who had never smoked ($p < .001$).

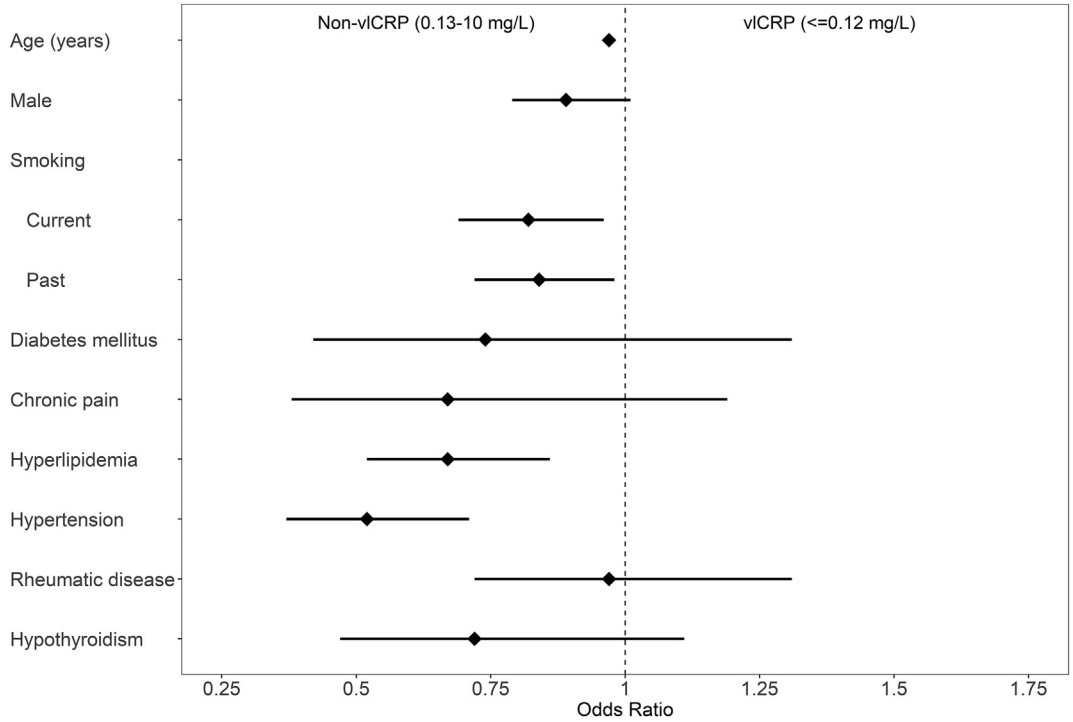

Fig. 2. The odds ratio for vlCRP (CRP ≤0.12 mg/L) in multivariable analysis.
*OR > 1 indicate higher probability for CRP ≤0.12 mg/L and OR < 1 indicate higher probability for CRP > 0.12 mg/L.

Table 4
CRP distribution in participants with CRP ≤0.12 mg/L at first evaluation: (A) Second evaluation, (B) All recurrent evaluations.

CRP (mg/L)	Second evaluation	All evaluations
	(A)	(B)
≤0.12	306 (50.1%)	608 (49.1%)
0.13–0.50	220 (36.0%)	438 (35.4%)
0.51–1.00	37 (6.1%)	85 (6.9%)
1.01–3.00	31 (5.1%)	69 (5.6%)
3.01–5.00	9 (1.5%)	23 (1.9%)
≥5.01	8 (1.3%)	15 (1.2%)

Participants with morbidities had lower rates of very low CRP. Very low CRP was less common in patients with diabetes mellitus (4.3% vs. 9.3%), chronic pains (5.4% vs. 9.3%), hyperlipidemia (5.0% vs. 9.6%), hypertension (3.4% vs 9.7%), rheumatic disease (6.8% vs. 9.3%) and hypothyroidism (1.8% vs. 9.3%), compare to participants without the morbidity.

In multivariable analysis, older age, hyperlipidemia, hypertension and smoking were associated with lower probability of very low CRP (Table 3, Fig. 2).

3.3. CRP level at second check-up in participants with very low CRP at their first visit

Six hundred and eleven participants with very low CRP at first evaluation visited our routine check-up program more than once and met the inclusion criteria in their next visits. Of them, 306 (50.1%) had very low CRP (≤0.12 mg/L) at their second visit and the rest of them had a median CRP level of 0.28 mg/L (IQR 0.18–0.58). CRP distribution in the second visit is presented in Table 4(a) and Fig. 3.

The median time between the first and the second visit was

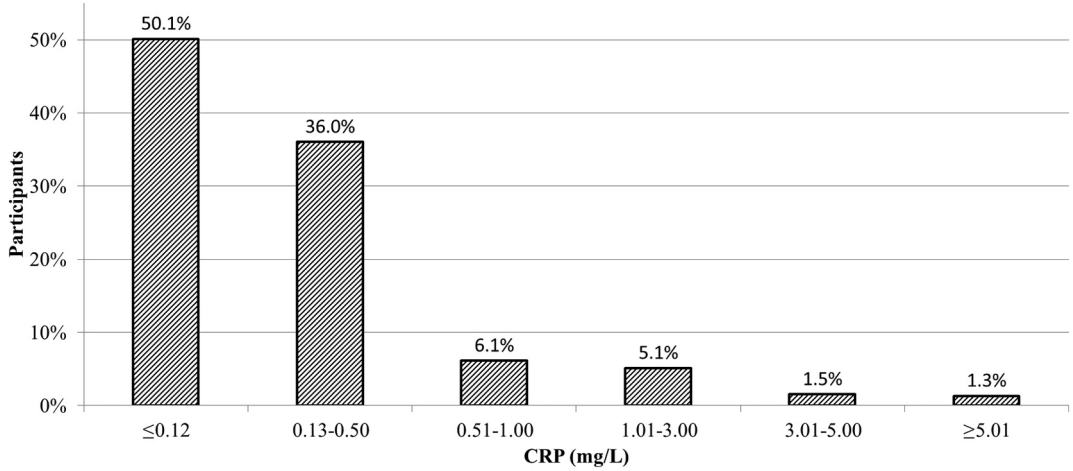

Fig. 3. CRP level at second evaluation in participants with CRP ≤0.12 mg/L at first evaluation.

2.34 years (IQR 1.49–4.01). None of the studied predictors at first visit was significantly associated with very low CRP at the second visit (Appendix 3).

3.4. CRP level at recurrent visits in participants with very low CRP at their first check-up

In total, these 611 participants with very low CRP at first evaluation had 1238 revisits for routine check-up. The median length of follow up was 4.35 years (range 0.91–13.92). Three hundred and ten participants (50.7%) had only one revisit, 23.4% had two revisits, 12.3% had three revisits and 13.6% had four revisits or more. In 608 (49.1%) of the 1238 revisits the CRP was very low (≤0.12 mg/L) and in the other evaluations the median CRP was 0.3 mg/L (IQR 0.19–0.65 mg/L). CRP distribution in the recurrent visits is presented in Table 4(b). Two hundred and twenty-nine (37.5%) participants had very low CRP in all their evaluations. Time that passed from the initial evaluation was not associated with vlCRP recurrence (OR 0.984, 95%CI 0.933–1.037, $p = .539$). In these participants, age ($p = .753$), gender ($p = .622$), smoking status ($p = .599$), cardiovascular disease ($p = .899$), diabetes mellitus ($p = .952$), chronic fatigue or fibromyalgia ($p = .685$), chronic pain ($p = .350$), hyperlipidemia ($p = .125$), hypertension ($p = .593$), inflammatory bowel disease ($p = .758$), peripheral vascular disease ($p = .592$), chronic lung disease ($p = .210$) and rheumatic disease ($p = .673$) were not associated with vlCRP, while hypothyroidism was associated with higher probability of vlCRP (OR 2.881, 95%CI 1.345–6.174, $p = .006$). In the laboratory tests exams, lower white blood cells count ($p = .014$), neutrophils percent ($p = .001$), neutrophil-to-lymphocyte ratio ($p = .001$) and lactate dehydrogenase ($p = .001$) were associated with vlCRP, while higher lymphocytes percent ($p = .006$) was associated with vlCRP. Hemoglobin ($p = .932$), creatinine ($p = .165$), platelet count ($p = .084$) and albumin ($p = .149$) were not associated with vlCRP.

3.5. CRP level at second check-up in participants without very low CRP at their first visit

Six thousand and thirty one participants with CRP > 0.12 mg/L at first evaluation visited our routine check-up program more than once and met the inclusion criteria in their next visits. In this population, the rate of participants with very low CRP (≤0.12 mg/L) at their second visit was significantly lower (6.6%) than that in participants with very low CRP at their first visit (50.1%, $p < .001$). The median time between the first and the second visit was 2.39 years (IQR 1.56–3.96).

4. Discussion

The study examined a large cohort of patients in order to evaluate the association between vlCRP, almost undetectable levels of CRP, and various health conditions in individuals who undergo a routine health examination. The study also aimed to describe the repetition of vlCRP in these patients.

The study showed that younger age, non-smoking, absence of hyperlipidemia and of hypertension are associated with vlCRP. From here, vlCRP is associated with better health status.

Some studies based on routine health examination cohorts used cut-off values < 1 mg/L to define vlCRP. These studies used high sensitivity CRP while we used wide range CRP. Previous studies showed that there is a good agreement between these methods [4,11]. A previous study showed that vlCRP is associated very lower probability of metabolic syndrome [13]. This study showed that vlCRP is associated with absence of hyperlipidemia.

While we did not find an association between vlCRP and cardiovascular disease, two previous studies did show such an association [8,22]. Other studies showed that vlCRP is associated with non-development of fatty liver, *Helicobacter pylory* seronegativity and absence of obstructive sleep apnea, however we did not have such data in our files and no participant in our cohort had documented liver disease [5,6,12].

Approximately, half of the individuals who presented vlCRP in their first visit also presented vlCRP at their next visit and in their all recurrent visits. However, we did not find any predictor at first evaluation which is associated with repetition of vlCRP in the second evaluation. When we studied all recurrent visits in individuals who presented vlCRP in their first visit, none of the morbidity at the time of evaluation except hypothyroidism was associated with vlCRP while some blood tests that are indicators for infections were associated with lower probability of vlCRP. Moreover, time from initial evaluation was not associated with vlCRP repetition. Hence, it is reasonable to conclude that the vlCRP is part of the subject's physiology.

Consumption of CRP by phospholipid containing particles, which can contribute to lowering of CRP was reported [23–25]. Therefore, there is a possibility that high affinity to plasma lipoproteins could explain, at least in part, the presence of low serum CRP concentrations. However, this could not be examined in the present study since we did not have detailed information about the concentration of the various fractions the patient's lipoproteins and thus could not examine the correlation, if any, with the serum CRP concentrations.

In this study individuals with CRP values associated with infectious status and individuals who reported taking statins were excluded in order to avoid potential biases. However, several limitations still exist. First, a number of medical conditions have been reported by the patients and therefore can be subjective and bare to reporting bias. However, we do not believe that there was a reason to divert the report. Second, the annual check-up evaluation in not part of the regular health services in our country and usually it is partially funded by private health insurance and workplaces. Therefore, we refer to our cohort as apparently healthy individuals. Third, not all patients returned to another check-up and the time between them was not fixed. In order to overcome this limitation, we first looked for predictor for vlCRP in the initial and following evaluations and used GEE model to study the further evaluations. Fourth, we could not define vlCRP using low percentile (such as 1, 2.5 or 5), since 9.2% of the participants had CRP ≤ 0.12 mg/L. According to Siemens Inc., the lower analytical range of wrCRP is 0.12 mg/L for ADVIA 1800/1650, commonly use clinical chemistry systems. Therefore, we used this almost undetectable level of CRP to define vlCRP. Fifth, a variation in the method unavoidably led to some misclassifications around the cut-off of 0.12 mg/L.

In conclusion, very low CRP is initially associated with younger age, non-smoking, and absence of hyperlipidemia and of hypertension. However, it may also be part of the individual physiology.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.04.073.

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