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Risk factors for coronary heart disease and acute-phase proteins

A population-based study

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Aims Circulating levels of C-reactive protein and serum amyloid A protein increase markedly, and albumin levels fall, during the acute-phase response to tissue injury, infection and inflammation. Some acute-phase proteins have been associated with increased risks of coronary heart disease in long-term prospective studies. The aim of the present study was to determine whether circulating concentrations of C-reactive protein, albumin and serum amyloid A protein are correlated with one another, standard vascular risk factors, markers of persistent infection, or indicators of socio-economic status.

Methods and Results We report a cross-sectional study of 704 individuals without a history of coronary heart disease from five general practices in Bedfordshire, U.K. Plasma levels of C-reactive protein and serum amyloid A protein were strongly associated with each other ($2P<0{\cdot}00001$) and inversely related to levels of serum albumin ($2P<0{\cdot}00001$). There were highly significant associations of plasma C-reactive protein concentrations with cigarette smoking and obesity ($2P<0{\cdot}00001$ for each). Serum albumin levels were strongly associated with blood pressure ($2P<0{\cdot}0001$) and plasma lipids ($2P<0{\cdot}001$), and concentrations of serum amyloid A protein were strongly correlated with obesity ($2P<0{\cdot}0001$).

Conclusion Previously reported long-term prospective studies have found an increased risk of coronary heart disease of about 50% in people with raised baseline levels of plasma C-reactive protein or low albumin. The strong cross-sectional associations we have found between levels of these proteins with each other and with concentrations of serum amyloid A protein suggest that some underlying process related to inflammation is likely to be of relevance to the causation of disease. Further studies are needed to determine if the strong associations of plasma levels of C-reactive protein with cigarette smoking and obesity indicate that this particular protein can mediate some of the effects of those risk factors on coronary heart disease.
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Key Words: Coronary heart disease, acute-phase proteins, C-reactive protein, albumin, serum amyloid A protein.

Introduction

Laboratory-based and epidemiological studies have investigated associations between coronary heart disease and plasma proteins involved in the acute-phase response to tissue damage or inflammation[1–3]. Levels of C-reactive protein, the classical acute-phase plasma protein, can rise by more than 1000-fold, whereas serum albumin levels can fall by about 20% following tissue damage[1]. In long-term prospective studies of coronary heart disease, a comparison of individuals in the top third with those in the bottom third of a single baseline measurement of C-reactive protein (corresponding to usual plasma levels of 2·4 vs 1·0 mg . l^{-1}) has yielded a combined risk ratio of 1·7 (95% confidence interval 1·4 to 2·1) after adjustment for standard risk factors[1]. In other prospective studies, a comparison of individuals in the bottom third with those in the top third of a single baseline measurement of albumin (corresponding to usual serum levels of 38 vs 42 g . l^{-1}, i.e., an inverse association) has yielded a combined risk ratio for coronary heart disease of 1·5 (1·3–1·7) after adjustment[1].

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The relevance of these factors to the causation of coronary heart disease, however, remains uncertain. Raised C-reactive protein levels or lowered albumin may merely reflect the extent and severity of atheroma, of which inflammation is an essential component. Alternatively, altered levels of these factors may be elicited by low-grade inflammation or infection elsewhere in the body which could be relevant to the causation of coronary heart disease. Another possibility is that the altered plasma protein profile during tissue damage, or the specific actions of particular acute-phase proteins, or both, might increase the incidence of coronary heart disease directly. To help distinguish between these possibilities, it is necessary to study acute-phase proteins, vascular risk factors, and possible confounders in apparently healthy individuals. There have been just two previous cross-sectional reports with details of C-reactive protein values and vascular risk factors, one in 300 British men[4] and the other in 400 elderly Americans[5]. They have made conflicting claims, particularly with respect to possible associations between C-reactive protein and smoking status or serum lipids, but the samples were relatively small and no attempts were made to avoid spurious associations arising from multiple comparisons. The only study of serum albumin and C-reactive protein reported on 500 individuals[6]. Here we report a larger scale, population-based study in 700 men and women involving measurement of C-reactive protein, albumin, standard risk factors and other relevant characteristics. We also measured serum amyloid A protein, an extremely sensitive acute phase reactant like C-reactive protein, which has not been studied before in relation to vascular risk factors.

Methods

Participants and laboratory methods

Eight thousand volunteers aged 35–64 at entry to a trial of health checks by nurses in Bedfordshire general practices completed questionnaires and gave venous blood samples that were centrifuged and stored at −80 °C[7]. Practice nurses made measurements of participants' height, weight, and blood pressure. In the samples of 704 individuals without a history of coronary heart disease who were randomly selected as controls for another study, measurements were made of concentrations of serum lipids and albumin using standard assays[7], of C-reactive protein and SAA using sensitive automated enzyme immunoassays[8,9], of IgG antibodies to *Helicobacter pylori* using a commercial kit (Orion, Pyloriset: Espoo, Finland), and of IgG antibodies, to *Chlamydia pneumoniae* (whole organism antigen) and to cytomegalovirus (whole organism antigen) using time-resolved fluorimetry (DELFIA®, Wallac: Turku, Finland). The coefficient of variation within C-reactive protein and serum amyloid A protein assays was about 4%; the variation between these assays was about 12%. In the sera of 480 individuals from another study, our measurements of *C. pneumoniae* antibodies agreed well with those made by standard microimmunofluorescence[10].

Statistics

Logarithmic transformation of C-reactive protein and serum amyloid A protein concentrations gave approximately symmetrical distributions. Analysis by thirds of the concentrations of C-reactive protein, albumin and serum amyloid A protein was pre-specified. Associations with vascular risk factors and other characteristics were investigated using t-tests, chi-square tests and regression modelling (STATA Corporation, Texas, U.S.A.). To reduce the possibility of spurious associations due to multiple comparisons, emphasis was given mainly to differences more extreme than 2·6 standard deviations ($2P \approx 0{\cdot}01$). For continuous variables, such as total serum cholesterol, the sample size was sufficient to detect differences of >5% with 80% power at the 1% level of significance; for dichotomous variables, such as *H. pylori* seropositivity, it was also sufficient to detect differences in prevalence of >5%.

Results

There were 704 participants, of whom 479 were men. When stratified by sex, the overall results were unchanged, so findings are presented as combined results for men and women.

Associations between acute-phase proteins

There were strong and highly significant associations between plasma levels of C-reactive protein and serum amyloid A protein ($R = 0{\cdot}74$; $2P < 0{\cdot}00001$), and highly significant inverse associations between each of these factors and levels of serum albumin ($R = -0{\cdot}20$ and $R = -0{\cdot}27$, respectively; $2P < 0{\cdot}00001$ for each) (Tables 1–3).

Standard risk factors and concentrations of acute-phase proteins

There were highly significant correlations between C-reactive protein values and smoking and obesity ($2P < 0{\cdot}00001$ for each: Table 1). Among smokers, C-reactive protein concentrations increased with increasing cigarette consumption ($2P < 0{\cdot}001$). Serum albumin levels were positively and highly significantly associated with blood pressure ($2P < 0{\cdot}0001$), male sex ($2P < 0{\cdot}001$) and serum concentrations of triglyceride ($2P < 0{\cdot}00001$), total cholesterol and low-density lipoprotein cholesterol ($2P < 0{\cdot}01$). Also, there was weak

Table 1 Vascular risk factors and other characteristics by thirds of C-reactive protein concentration

Characteristic	Thirds of C-reactive protein concentration (mg . l^{-1})			t^{+}	t^{++}
	<0·90 (median 0·40)	0·91–2·80 (median 1·60)	≥2·81 (median 6·85)		
Standard vascular risk factors					
Age (years) n=704)	58·1 ± 6·4	58·8 ± 6·1	60·0 ± 5·4	3·8	1·8
Male (n=704)	172 (69%)	160 (69%)	143 (65%)	1·0	1·2
Current smokers (n=704)	54 (22%)	59 (25%)	90 (41%)	5·7	6·1***
Body mass index (kg . m^{-2}) (n=703)	25·0 ± 3·3	26·2 ± 3·4	27·1 ± 4·3	6·5	7·1***
Total cholesterol (mmol . l^{-1}) (n=701)	6·17=1·20	6·43 ± 1·18	6·40 ± 1·33	1·4	0·0
Low-density lipoprotein cholesterol (mmol . l^{-1}) (n=640)	3·93 ± 0·99	4·11 ± 0·98	4·09 ± 0·96	0·5	0·5
High-density lipoprotein cholesterol (mmol . l^{-1}) (n=692)	1·40 ± 0·43	1·31 ± 0·34	1·24 ± 0·34	3·9	1·9
Triglycerides (mmol . l^{-1}) (n=701)	2·00 ± 1·42	2·18 ± 1·28	2·31 ± 1·26	2·0	0·1
Systolic blood pressure (mmHg) (n=704)	131 ± 19	136 ± 22	140 ± 22	3·9	1·6
Diastolic blood pressure (mmHg) (n=704)	77 ± 12	80 ± 12	80 ± 13	2·6	1·3
Alcohol (units/week) (n=704)	9·7 ± 18·1	8·5 ± 13·9	6·8 ± 11·9	1·8	2·3
Physically inactive (n=704)	179 (72%)	162 (70%)	179 (81%)	2·3	0·8
Acute-phase proteins					
Albumin (g . l^{-1}) (n=642)	42·1 ± 2·8	42·2 ± 2·9	41·0 ± 3·4	6·3	5·2***
Log_eserum amyloid A (mg . l^{-1}) (n=704)	− 0·25 ± 1·27	0·71 ± 0·66	1·49 ± 1·15	29	28***
Markers of persistent infection					
Chlamydia pneumoniae titres (FC × 10^6) (n=676)	95·7 ± 41·3	105·0 ± 38·2	106·4 ± 38·9	3·7	2·8*
Helicobacter pylori seropositive (n=641)	69 (37%)	115 (50%)	110 (50%)	2·2	0·7
Cytomegalovirus titres (FC × 10^6) (n=676)	76·2 ± 54·1	84·0 ± 59·3	95·0 ± 58·4	3·7	1·8
Markers of socioeconomic status					
Without own car (n=699)	36 (14%)	38 (17%)	50 (23%)	1·9	1·2
In rented housing (n=694)	26 (11%)	42 (18%)	41 (19%)	1·6	0·9
Completed education by 16 years (n=692)	199 (81%)	207 (90%)	189 (87%)	2·5	1·1
Employed (n=700)	183 (74%)	150 (65%)	124 (56%)	3·6	3·0*
Manual workers (n=655)	97 (39%)	98 (42%)	95 (43%)	1·9	0·9
Married (n=692)	205 (35%)	197 (34%)	180 (31%)	1·0	0·7

FC=Fluorescence counts.
*$2P$<0·01. ***$2P$<0·00001.
$^{+}$t-tests derived from regression of log_eC-reactive protein concentration on each characteristic separately.
$^{++}$t-tests derived from regression of log_eC-reactive protein concentration adjusting for sex, age and body mass index (as continuous variables), smoking (current smoker, former smoker, current tobacco consumption, and pack years as continuous variables), and social class (car ownership, housing tenure, age at stopping full-time education, employment status, job classification, and marital status). Adjustments for social class were omitted in the regressions involving markers of socioeconomic status.

evidence of inverse associations of serum albumin levels with smoking and with concentrations of high-density lipoprotein cholesterol (Table 2). For serum amyloid A protein, there was a strong and highly significant association with obesity ($2P$<0·00001), and some evidence of association with smoking ($2P$<0·01: Table 3).

Markers of persistent infection, indicators of social class and plasma concentrations of C-reactive protein and of serum amyloid A protein

There were no strong associations between C-reactive protein values and levels of serum IgG antibody to cytomegalovirus or *H. pylori*. A significant correlation with *C. pneumoniae* IgG titres was markedly diminished following adjustment for age, sex, obesity, and social class. There were no consistent correlations between levels of C-reactive protein, albumin or serum amyloid A protein and indicators of social class.

Discussion

Previously reported meta-analyses have indicated that the risk of coronary heart disease increased by about 50% in people who, about 5 to 10 years before the onset of clinical disease (even after adjustment for the standard vascular risk factors[1]) had raised levels of plasma C-reactive protein or low levels of serum albumin. These associations, however, do not establish whether C-reactive protein or low albumin levels are responses to the extent and severity of pre-existing atherosclerosis, or markers for risk factors, or indicators of an underlying process such as persistent infection[11], or whether they are themselves mediators of vascular damage. Measurement of acute-phase proteins and risk factors, or possible confounders, in large samples is needed to help demonstrate whether such associations are causal or due to confounding.

The present population-based study in 700 people showed strong and highly significant associations of circulating concentrations of C-reactive protein, serum amyloid A protein, and low albumin with one another in

Table 2 Vascular risk factors and other characteristics by thirds of albumin concentration

Characteristic	Thirds of albumin concentration ($g \cdot l^{-1}$)			t^{+}	t^{++}
	<41 (median 39)	41–43 (median 42)	>43 (median 45)		
Standard vascular risk factors					
Age (years) (n=642)	59·7 ± 5·9	58·8 ± 5·9	58·3 ± 6·4	2·9	1·7
Male (n=642)	123 (58%)	146 (69%)	165 (79%)	4·3	3·3**
Current smokers (n=642)	75 (36%)	61 (29%)	51 (23%)	2·3	2·2
Body mass index ($kg \cdot m^{-2}$) (n=641)	25·9 ± 4·1	26·0 ± 3·6	26·5 ± 3·6	1·9	1·7
Total cholesterol ($mmol \cdot l^{-1}$) (n=640)	6·22 ± 1·14	6·40 ± 1·07	6·41 ± 1·27	1·9	3·1*
Low-density lipoprotein cholesterol ($mmol \cdot l^{-1}$) (n=587)	3·94 ± 0·93	4·08 ± 0·91	4·11 ± 1·10	1·9	2·7*
High-density lipoprotein cholesterol ($mmol \cdot l^{-1}$) (n=633)	1·39 ± 0·38	1·31 ± 0·39	1·25 ± 0·36	3·8	2·5
Triglycerides ($mmol \cdot l^{-1}$) (n=640)	1·81 ± 0·92	2·18 ± 1·25	2·46 ± 1·59	5·5	5·1***
Systolic blood pressure (mmHg) (n=642)	133 ± 21	135 ± 22	138 ± 23	2·6	3·3**
Diastolic blood pressure (mmHg) (n=642)	76 ± 12	79 ± 12	82 ± 12	5·2	4·4***
Alcohol (units/week) (n=642)	7·6 ± 15	9·1 ± 17	8·6 ± 13	1·2	0·1
Physically inactive (n=642)	160 (76%)	156 (74%)	159 (73%)	1·1	1·9
Acute-phase proteins					
Log_eC-reactive protein ($mg \cdot l^{-1}$) (n=642)	0·90 ± 1·31	0·58 ± 1·18	0·33 ± 1·17	6·3	5·2***
Log_eserum amyloid A protein ($mg \cdot l^{-1}$) (n=642)	1·21 ± 1·14	0·82 ± 0·80	0·65 ± 0·79	7·0	6·0***
Markers of persistent infection					
Chlamydia pneumoniae titres (FC × 10^6) (n=641)	106·7 ± 40·0	99·5 ± 40·3	104·1 ± 37·5	0·7	1·0
Helicobacter pylori seropositive (n=638)	105 (50%)	100 (48%)	89 (41%)	1·1	0·5
Cytomegalovirus titres (FC × 10^6) (n=641)	92·2 ± 54·5	81·8 ± 58·7	82·9 ± 59·9	0·5	0·8
Markers of socioeconomic status					
Without own car (n=637)	45 (21%)	38 (18%)	31 (14%)	1·2	0·6
In rented housing (n=633)	39 (19%)	35 (17%)	31 (14%)	1·8	1·4
Completed education by 16 years (n ± 631)	178 (86%)	181 (87%)	185 (86%)	0·5	0·2
Employed (n=638	110 (52%)	143 (68%)	159 (73%)	2·8	2·6*
Manual workers (n=642)	157 (74%)	153 (72%)	141 (64%)	1·5	1·3
Married (n=631)	176 (84%)	169 (82%)	188 (87%)	1·0	0·8

FC=Fluorescence counts.
*$2P<0·01$. **$2P<0·001$. ***$2P<0·0001$.
$^{+}$t-tests derived from regression of albumin concentration on each characteristic separately.
$^{++}$t-tests derived from regression of albumin concentration adjusting for sex, age and body mass index (as continuous variables), smoking (current smoker, former smoker, current tobacco consumption, and pack years as continuous variables), and social class (car ownership, housing tenure, age at stopping full-time education, employment status, job classification, and marital status). Adjustments for social class were omitted in the regressions involving markers of socioeconomic status.

free-living individuals, even after adjustment for age, sex, smoking, obesity and markers of social class. It is very unlikely that these associations merely reflect chronic illness, as participants had no history of coronary heart disease and the findings were largely unchanged when the few individuals were excluded who had a history of cancer, diabetes or other chronic diseases. As circulating levels of several acute-phase reactants, such as C-reactive protein, low albumin, fibrinogen or leucocyte count, have been separately associated with increased risk of coronary heart disease[1], our finding of a close association between levels of C-reactive protein, albumin and serum amyloid A protein with one another increases the likelihood that there is some underlying process related to inflammation which is relevant to the causation of the disease. However, although it has been suggested that chronic low-grade infection, with *H. pylori*, *C. pneumoniae*, or cytomegalovirus may be associated with coronary heart disease, and also with a persistent acute-phase response[4], we found no consistent or strong evidence of associations between serological evidence of these infective agents and levels of C-reactive protein, albumin or serum amyloid A protein.

As regards C-reactive protein, our study sample is about twice as large as each of the previous reports on risk factors, and should be more representative of the general population than either of those reports since it involves a community-based sample of middle-aged British men and women[4,5]. We found strong and highly significant associations of C-reactive protein values with cigarette smoking and with obesity. As C-reactive protein levels are higher in active smokers than in non-smokers, and increase with increasing cigarette consumption, it is possible that C-reactive protein may mediate at least part of the effect of smoking on coronary heart disease, perhaps by proatherogenic interactions with low density lipoprotein[12] or in a procoagulant manner by stimulating tissue factor production by macrophages[13]. The same considerations apply with respect to obesity, in which raised C-reactive protein values may reflect increased production of cytokines[14,15]. We found no evidence of strong correlations between C-reactive protein values and

Table 3 Vascular risk factors and other characteristics by thirds of serum amyloid A protein concentration

Characteristic	Thirds of serum amyloid A concentration (mg . l^{-1})			t^{+}	t^{++}
	<0·99 (median 0·90)	1·00–2·99 (median 2·00)	≥3·00 (median 5·00)		
Standard vascular risk factors					
Age (years) (n=704)	58·3 ± 6·5	59·1 ± 5·8	59·5 ± 5·8	1·9	1·5
Male (n=704)	176 (75%)	177 (71%)	122 (56%)	3·2	2·0
Current smokers (n=704)	61 (26%)	78 (31%)	64 (29%)	1·5	2·8*
Body mass index (kg . m^{-2}) (n=703)	25·1 ± 3·2	26·0 ± 3·2	27·3 ± 4·5	4·8	5·0***
Total cholesterol (mmol . l^{-1}) (n=701)	6·12 ± 1·12	6·44 ± 1·12	6·52 ± 1·25	0·9	0·6
Low-density lipoprotein cholesterol (mmol . l^{-1}) (n=640)	3·88 ± 0·95	4·12 ± 0·97	4·11 ± 1·01	0·9	0·3
High-density lipoprotein cholesterol (mmol . l^{-1}) (n=692)	1·33 ± 0·39	1·29 ± 0·36	1·34 ± 0·40	0·2	0·9
Triglycerides (mmol . l^{-1}) (n=701)	1·97 ± 1·20	2·30 ± 1·43	2·19 ± 1·31	0·4	1·7
Systolic blood pressure (mmHg) (n=704)	133 ± 22	135 ± 20	139 ± 22	2·4	1·2
Diastolic blood pressure (mmHg) (n=704)	78 ± 11	79 ± 12	81 ± 13	2·0	1·1
Alcohol (units/week) (n=704)	8·8 (15·4)	9·2 (14·5)	7·0 (15·1)	1·2	0·3
Physically inactive (n=704)	168 (71%)	185 (74%)	167 (77%)	1·7	0·7
Acute-phase proteins					
Log_eC-reactive protein (mg . l^{-1}) (n=704)	− 0·65 ± 1·32	0·38 ± 1·01	1·39 ± 1·21	29	28***
Albumin (g . l^{-1}) (n=642)	42·5 ± 3·1	42·1 ± 2·7	40·8 ± 3·3	7·0	6·0***
Markers of persistent infection					
Chlamydia pneumoniae titres (FC × 10^6) (n=676)	98·4 ± 41·6	104·3 ± 37·9	104·0 ± 39·7	2·8	2·4
Helicobacter pylori seropositive (n 641)	76 (43%)	110 (44%)	108 (50%)	1·6	1·0
Cytomegalovirus (FC × 10^6) (n=676)	85·2 ± 57·0	83·6 ± 58·2	86·5 ± 58·2	0·5	0·9
Markers of socioeconomic status					
Without own car (n=699)	38 (16%)	44 (18%)	42 (19%)	0·7	0·2
In rented housing (n=694)	27 (12%)	40 (16%)	42 (20%)	1·1	0·8
Completed education by 16 years (n=692)	191 (83%)	212 (85%)	192 (90%)	2·0	1·2
Employed (n=700)	171 (73%)	158 (63%)	128 (59%)	4·1	2·6*
Manual workers (n=655)	98 (42%)	102 (41%)	90 (41%)	2·0	0·4
Married (n=692)	196 (85%)	206 (84%)	180 (84%)	0·4	0·1

FC=Fluorescence counts.
*2P<0·01. ***2P<0·00001.
$^{+}$t-tests derived from regression of log_eserum amyloid A concentration of each characteristic separately.
$^{++}$t-tests derived from regression of log_eserum amyloid A concentration adjusting for sex, age and body mass index (as continuous variables), smoking (current smoker, former smoker, current tobacco consumption, and pack years as continuous variables), and social class (car ownership, housing tenure, age at stopping full-time education, employment status, job classification, and marital status). Adjustments for social class were omitted in the regressions involving markers of socioeconomic status.

concentrations of plasma lipids, blood pressure, *H. pylori* seropositivity, or indicators of social class. Previous claims[4,16] of such associations in smaller studies were probably due to chance, or incomplete adjustment for possible confounders, or both. The correlation between C-reactive protein values and *C. pneumoniae* IgG titres weakened substantially in our study following adjustment for confounders, and previous reports have been limited by small samples, insensitive assays, or both[4,17], indicating that larger studies are needed to determine whether such an association exists.

Positive associations between serum albumin levels and male sex, serum lipids and blood pressure, or inverse associations between serum albumin levels and age and smoking have been reported in previous studies[18–20]. Most, however, have considered serum albumin values only in relation to a few risk factors and did not adjust for possible confounders. The present results include adjustment for possible confounders and confirm the existence of several such associations in a single population. Positive associations of serum albumin values with blood pressure or with serum lipid concentrations indicate that these variables cannot distort the association between low serum albumin levels and coronary heart disease. Mechanisms proposed to account for this association include reduced serum anti-oxidant activity[2] and impaired endothelium derived relaxing factor-like activity[22], but no direct evidence is available. With regard to serum amyloid A protein, there is little information from either prospective[23] or cross-sectional[24] studies on its relationship to coronary heart disease, and work is needed to find out if serum amyloid A protein production is associated with clinical disease. This report provides the first detailed investigation of plasma serum amyloid A protein concentrations and risk factors, and it indicates strong correlations with obesity and, perhaps, with smoking, but not with the other standard risk factors described here.

We have reported two main findings. First, we observed strong and highly significant associations of circulating levels of C-reactive protein, serum amyloid A protein and low albumin with one another. Together with the previous evidence on associations between coronary heart disease and circulating levels of

C-reactive protein and low albumin, the close association among these acute-phase proteins in apparently healthy people suggests that some process related to inflammation is likely to be relevant to the causation of coronary heart disease. Second, we observed strong epidemiological associations of plasma C-reactive protein concentrations with smoking and obesity, suggesting that C-reactive protein could be involved in the pathways by which these factors increase the risk of coronary heart disease. As there may be substantial fluctuation in the circulating levels of acute-phase proteins within individuals over time[1], future studies should aim to involve large samples with serial measurements of the relevant proteins, as well as measurement of additional confounders, potential mediators, and other possible risk factors[2,25].

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