

## Chronic inflammation as a determinant of future aging phenotypes

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### ABSTRACT

**Background:** The importance of chronic inflammation as a determinant of aging phenotypes may have been underestimated in previous studies that used a single measurement of inflammatory markers. We assessed inflammatory markers twice over a 5-year exposure period to examine the association between chronic inflammation and future aging phenotypes in a large population of men and women.

**Methods:** We obtained data for 3044 middle-aged adults (28.2% women) who were participating in the Whitehall II study and had no history of stroke, myocardial infarction or cancer at our study's baseline (1997–1999). Interleukin-6 was measured at baseline and 5 years earlier. Cause-specific mortality, chronic disease and functioning were ascertained from hospital data, register linkage and clinical examinations. We used these data to create 4 aging phenotypes at the 10-year follow-up (2007–2009): successful aging (free of major chronic disease and with optimal physical, mental and cognitive functioning), incident fatal or nonfatal cardiovascular disease, death from noncardiovascular causes and normal aging (all other participants).

**Results:** Of the 3044 participants, 721 (23.7%) met the criteria for successful aging at the 10-year follow-up, 321 (10.6%) had cardiovascular disease events, 147 (4.8%) died from noncardiovascular causes, and the remaining 1855 (60.9%) were included in the normal aging phenotype. After adjustment for potential confounders, having a high interleukin-6 level ( $> 2.0$  ng/L) twice over the 5-year exposure period nearly halved the odds of successful aging at the 10-year follow-up (odds ratio [OR] 0.53, 95% confidence interval [CI] 0.38–0.74) and increased the risk of future cardiovascular events (OR 1.64, 95% CI 1.15–2.33) and noncardiovascular death (OR 2.43, 95% CI 1.58–3.80).

**Interpretation:** Chronic inflammation, as ascertained by repeat measurements, was associated with a range of unhealthy aging phenotypes and a decreased likelihood of successful aging. Our results suggest that assessing long-term chronic inflammation by repeat measurement of interleukin-6 has the potential to guide clinical practice.

**Competing interests:** None declared.

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Chronic inflammation has been implicated in the pathogenesis of age-related conditions,<sup>1</sup> such as type 2 diabetes,<sup>2,3</sup> cardiovascular disease,<sup>4</sup> cognitive impairment<sup>5</sup> and brain atrophy.<sup>6</sup> Chronic inflammation may result from or be a cause of age-related disease processes (illustrated in Appendix 1, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1)). For example, obesity increases inflammation, and chronic inflammation, in turn, contributes to the development of type 2 diabetes by inducing insulin resistance,<sup>7,8</sup> and to coronary artery disease by promoting atherogenesis.<sup>9</sup> Thus, raised levels of inflammation appear to be implicated in various pathological processes leading to diseases in older age.

Of the various markers of systemic inflammation, interleukin-6 is particularly relevant to aging outcomes. There is increasing evidence

that interleukin-6 is the pro-inflammatory cytokine that “drives” downstream inflammatory markers, such as C-reactive protein and fibrinogen.<sup>10,11</sup> Interleukin-6, in contrast to C-reactive protein and fibrinogen, is also likely to play a causal role in aging owing to its direct effects on the brain and skeletal muscles.<sup>12,13</sup> In addition, results of Mendelian randomization studies of interleukin-6 and studies of antagonists are consistent with a causal role for interleukin-6 in relation to coronary artery disease, again in contrast to C-reactive protein and fibrinogen.<sup>14</sup>

However, current understanding of the link between chronic inflammation and aging phenotypes is hampered by the methodologic limitations of many existing studies. Most studies reported an assessment of inflammation based on a single measurement, precluding a distinction between the short-term (acute) and longer-term

(chronic) impact of the inflammatory process on disease outcomes.<sup>7</sup> We conducted a study using 2 measurements of interleukin-6 obtained about 5 years apart to examine the association between chronic inflammation and aging phenotypes assessed 10 years later in a large population of men and women. Because inflammation characterizes a wide range of pathological processes, we considered several aging phenotypes, including cardiovascular disease (fatal and nonfatal), death from noncardiovascular causes and successful aging (optimal functioning across different physical, mental and cognitive domains).

## Methods

### Study population

We selected participants from the Whitehall II study cohort, established in 1985 among 10 308 British civil servants (67% men).<sup>15</sup> In brief, all civil servants aged 35–55 years in 20 government departments based in London, UK, were

invited to participate in the Whitehall II study; 73% agreed. The study consists of a nurse-administered clinical examination about every 5 years (1985–1988, 1991–1993, 1997–1999, 2002–2004 and 2007–2009). It was approved by the University College London Ethics Committee, and all participants gave written consent.

To allow follow-up beyond age 60, we included participants who were 49 years or older in 1997–1999 (the baseline for our study). We restricted the study population to the 3044 participants who had no history of stroke, myocardial infarction or cancer at baseline and for whom complete data were available on aging phenotypes at 10-year follow-up (2007–2009), inflammatory markers at baseline and 5 years before baseline (1991–1993), and main covariates at baseline. A flow chart depicting the selection of participants is shown in Figure 1.

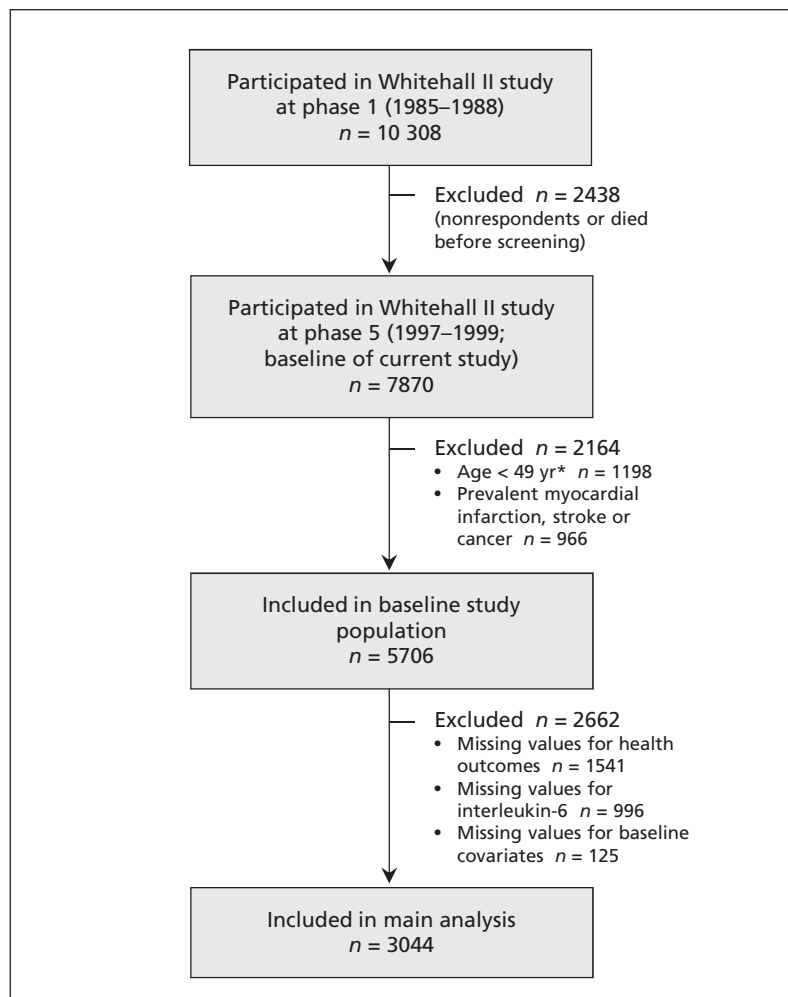
### Assessment of inflammatory markers

Interleukin-6, a marker of systemic inflammation, was measured with use of a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems).<sup>16</sup> At both the 1991–1993 and 1997–1999 clinical examinations, blood samples were collected between 8 am and 1 pm, stored at  $-80^{\circ}\text{C}$  and were not thawed or refrozen during storage. Stored serum samples from both phases were analyzed in the same laboratory. Interleukin-6 values below the detection limit (0.08 ng/L) were assigned a value equal to half the detection limit. Coefficients of variation were 7.5%. The reliability of values across follow-up examinations, assessed with Spearman correlation coefficients, was 0.46.

C-reactive protein was also measured, with use of an immunonephelometric assay (BN ProSpec nephelometer, Dade Behring).<sup>16</sup>

### Baseline covariates

We obtained sociodemographic data on the participants' sex, age and socioeconomic status (a 3-level measure of low, intermediate or high status based on civil service employment grade<sup>15</sup>). Health behaviours considered in the analyses were smoking status (never, former or current) and physical activity (inactive, moderately active or active) assessed by 20 questionnaire items on frequency and duration of participation in different activities, as detailed elsewhere.<sup>17</sup> Participants' health status included use of anti-inflammatory medication and possible cases of acute inflammation. Use of anti-inflammatory medication was determined from details provided by participants regarding their medication use (generic name, brand name or both). Possible cases of acute inflammation and immune



**Figure 1: Selection of participants for the current analyses from the Whitehall II study cohort. \*Age cutoff chosen to allow follow-up beyond age 60 for surviving participants.**

activation due to current illness were defined as having a C-reactive protein level greater than 10 mg/L.

### Outcome measures

Four aging phenotypes at the 10-year follow-up were considered: successful aging (free of major chronic disease and with optimal physical, mental and cognitive functioning); fatal or nonfatal (clinically verified coronary artery disease, including myocardial infarction, definite angina and self-reported stroke) cardiovascular disease events; death from noncardiovascular causes; and normal aging (all participants not included in the

other phenotypes).<sup>17</sup> We ascertained these health outcomes using data from 2 follow-up screenings (2002–2004 and 2007–2009) plus records from national health registers. Further information on the categorization of aging phenotypes is provided in Appendix 2 (available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1)).

### Statistical analysis

We grouped the interleukin-6 levels measured 5 years before baseline and at baseline into 3 categories:<sup>18</sup> low ( $\leq 1.0$  ng/L,  $n = 756$ ), intermediate (1.1–2.0 ng/L,  $n = 1456$ ) and high ( $> 2.0$  ng/L,  $n = 832$ ). There are currently no clinical thresh-

**Table 1:** Baseline characteristics of participants grouped according to aging phenotype at the 10-year follow-up

Characteristic	Outcome; no. (%) or mean $\pm$ SD at baseline					<i>p</i> value†
	All <i>n</i> = 3044	Successful aging* <i>n</i> = 721	Normal aging <i>n</i> = 1855	Fatal or nonfatal CVD event <i>n</i> = 321	Non-CVD death <i>n</i> = 147	
Age, yr	57.1 $\pm$ 5.2	56.1 $\pm$ 5.0	56.9 $\pm$ 5.1	59.6 $\pm$ 5.2	59.5 $\pm$ 5.3	0.001
Sex, female	818 (26.9)	180 (25.0)	533 (28.7)	59 (18.4)	46 (31.3)	0.006
Socioeconomic status						
Low	371 (12.2)	41 (5.7)	266 (14.3)	38 (11.8)	26 (17.7)	< 0.001
Intermediate	1275 (41.9)	269 (37.3)	807 (43.5)	140 (43.6)	59 (40.1)	
High	1398 (45.9)	411 (57.0)	782 (42.2)	143 (44.5)	62 (42.2)	
Smoking status						
Never	1580 (51.9)	409 (56.7)	957 (51.6)	152 (47.4)	62 (42.2)	< 0.001
Former	1213 (39.8)	276 (38.3)	739 (39.8)	139 (43.3)	59 (40.1)	
Current	251 (8.2)	36 (5.0)	159 (8.6)	30 (9.3)	26 (17.7)	
Physical activity						
Inactive	852 (28.0)	167 (23.2)	547 (29.5)	88 (27.4)	50 (34.0)	0.007
Moderately active	519 (17.0)	122 (16.9)	322 (17.4)	47 (14.6)	28 (19.0)	
Active	1673 (55.0)	432 (59.9)	986 (53.2)	186 (57.9)	69 (46.9)	
Use of anti-inflammatory drugs	295 (9.7)	37 (5.1)	193 (10.4)	41 (12.8)	24 (16.3)	< 0.001
Acute inflammation	86 (2.8)	9 (1.2)	60 (3.2)	13 (4.0)	4 (2.7)	0.02
Obesity‡	361 (11.9)	46 (6.4)	249 (13.4)	40 (12.5)	26 (17.7)	< 0.001
Use of lipid-lowering drugs‡	75 (2.5)	15 (2.1)	46 (2.5)	11 (3.4)	3 (2.0)	0.4
Interleukin-6 level§ at baseline						
Low	756 (24.8)	257 (35.6)	431 (23.2)	49 (15.3)	19 (12.9)	< 0.001
Intermediate	1456 (47.8)	344 (47.7)	896 (48.3)	158 (49.2)	58 (39.5)	
High	832 (27.3)	120 (16.6)	528 (28.5)	114 (35.5)	70 (47.6)	
No. of times interleukin-6 level was high over 5-yr exposure period¶						
0	1867 (61.3)	526 (73.0)	1110 (59.8)	164 (51.1)	67 (45.6)	< 0.001
1	791 (26.0)	145 (20.1)	507 (27.3)	98 (30.5)	41 (27.9)	
2	386 (12.7)	50 (6.9)	238 (12.8)	59 (18.4)	39 (26.5)	

Note: CVD = cardiovascular disease, SD = standard deviation.

\*Free of major chronic disease and with optimal physical, mental and cognitive functioning.

†For comparisons among the 4 outcome groups;  $\chi^2$  test for categorical variables and Student *t* test for age.

‡Values for body mass index were missing for 373 participants; values for use of lipid-lowering drugs were missing for 10 participants.

§Low =  $\leq 1.0$  ng/L, intermediate = 1.1–2.0 ng/L, high =  $> 2.0$  ng/L.

¶Interleukin-6 was measured twice (5 yr before baseline and at baseline); 0 = neither measurement was high, 1 = either measurement was high, 2 = both measurements were high.

olds for interleukin-6; therefore, these thresholds are the ones used previously in the Whitehall II study.<sup>18</sup> The number of times each participant had a high interleukin-6 level over the 5-year exposure period (0, 1 or 2 times) was the measure used to assess chronic inflammation.<sup>18</sup>

We used logistic regression models to assess the association between interleukin-6 levels (at baseline and over the 5-year exposure period) and each aging phenotype. Each phenotype was coded as a dichotomous variable: successful aging (v. normal aging, cardiovascular and non-cardiovascular death phenotypes combined), fatal and nonfatal cardiovascular disease events (v. successful and normal aging phenotypes combined) and noncardiovascular death (v. successful and normal aging phenotypes combined). Analyses were first adjusted for sex and age and further adjusted for socioeconomic status, health behaviours, acute inflammation and use of anti-inflammatory drugs. These analyses were repeated using C-reactive protein levels as the marker of inflammation. Further logistic regression models were performed specifically to examine the association between interleukin-6 levels and each component of successful aging (good cardiovascular, respiratory, musculoskeletal and cognitive functioning, good mental well-being, and absence of diabetes, cancer and disability). This analysis was restricted to participants in the normal or successful aging phenotypes.

As reported in Appendix 3 (available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1)), we ran several sensitivity analyses to examine potential competing risk bias and the effect of sample selection and missing data on the associations. We used net reclassification improvement statistics to test the extent to which assessing the level of interleukin-6 twice, as compared with a single measurement, provided a stronger predictor of future aging phenotypes.<sup>19,20</sup>

All analyses were conducted using the SAS version 9 (SAS Institute).

## Results

Of the 3044 participants included in our study, 721 (23.7%) met the criteria for successful aging at the 10-year follow-up, 321 (10.6%) had cardiovascular disease events (42 fatal and 279 non-fatal), and 147 (4.8%) died from noncardiovascular causes. The remaining 1855 (60.9%) were included in the normal aging phenotype. Characteristics of the participants were compared across these 4 aging phenotypes (Table 1). Compared with the normal aging group, participants in the successful aging group were more likely to have low interleukin-6 levels at baseline, whereas those who had a cardiovascular disease event or died from noncardiovascular causes were more likely to have high interleukin-6 levels.

Interleukin-6 levels at baseline and over the 5-year exposure period were significantly associ-

**Table 2:** Sex- and age-adjusted association between interleukin-6 levels at baseline and over the 5-year exposure period and aging phenotypes at 10-year follow-up\*

Variable	Successful aging† n = 721		Fatal or nonfatal CVD event n = 321		Non-CVD death n = 147	
	No. of patients	OR (95% CI)	No. of patients	OR (95% CI)	No. of patients	OR (95% CI)
Interleukin-6 level‡ at baseline						
Low (ref)	257	1.00	49	1.00	19	1.00
Intermediate	344	0.64 (0.53–0.78)	158	1.47 (1.04–2.06)	58	1.39 (0.81–2.36)
High	120	0.36 (0.28–0.46)	114	1.97 (1.37–2.82)	70	3.06 (1.80–5.18)
No. of times interleukin-6 level was high over 5-yr exposure period§						
0 (ref)	526	1.00	164	1.00	67	1.00
1	145	0.58 (0.47–0.72)	98	1.47 (1.12–1.93)	41	1.48 (0.99–2.21)
2	50	0.42 (0.31–0.58)	59	1.54 (1.30–2.35)	39	2.75 (1.80–4.20)

Note: CI = confidence interval, CVD = cardiovascular disease, OR = odds ratio, ref = reference group.

\*Age- and sex-adjusted logistic regression assessed associations of inflammation with 3 outcomes: successful aging (v. normal aging, CVD event and non-CVD death phenotypes combined), total n = 3044; fatal or nonfatal CVD event (v. successful and normal aging phenotypes combined), total n = 2897 (excludes 147 participants who had a non-CVD death); and non-CVD death (v. successful and normal aging phenotypes combined), total n = 2723 (excludes 321 participants who had CVD event).

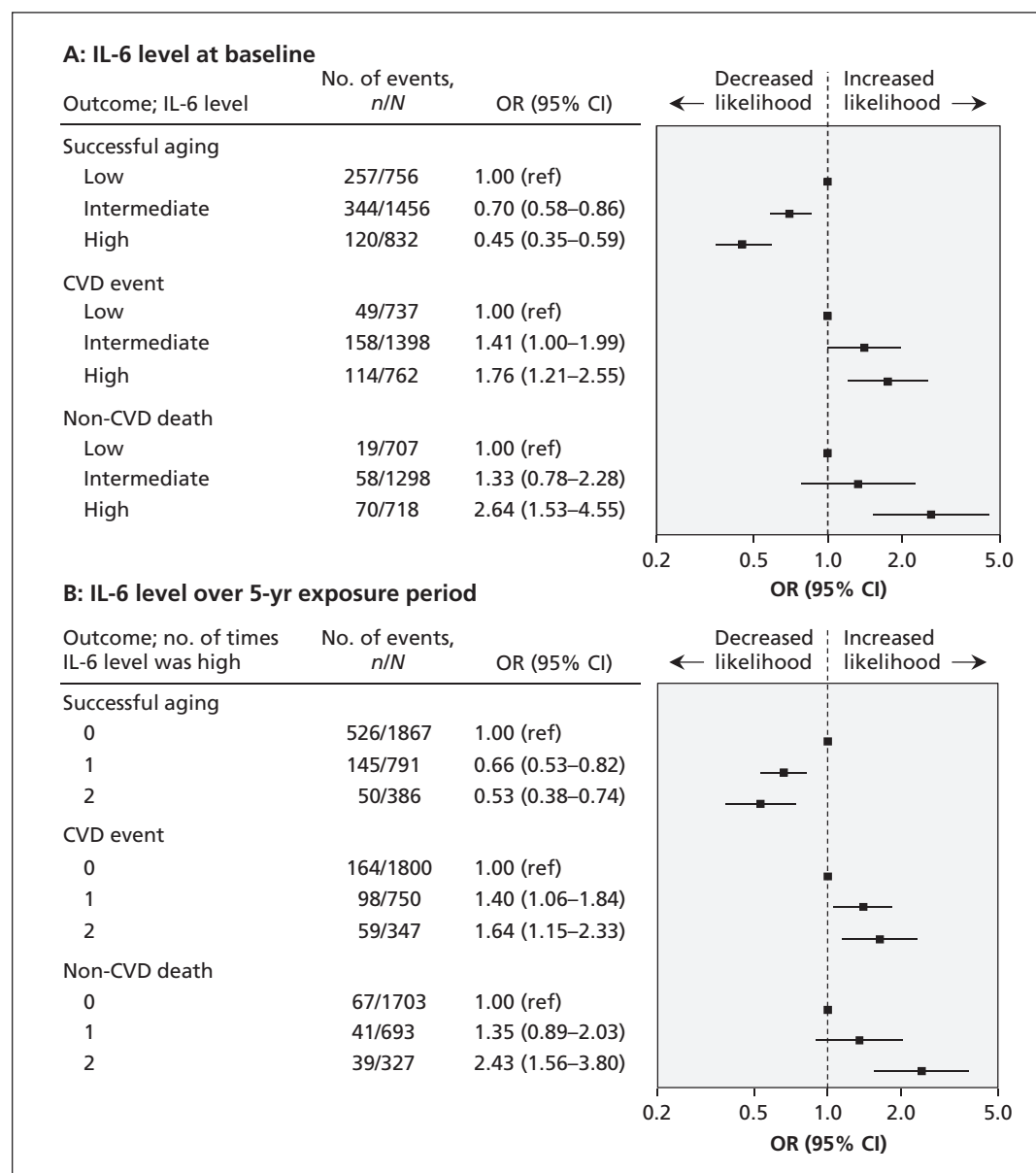
†Free of major chronic disease and with optimal physical, mental and cognitive functioning.

‡Low = ≤ 1.0 ng/L, intermediate = 1.1–2.0 ng/L, high = > 2.0 ng/L.

§Interleukin-6 was measured twice (5 yr before baseline and at baseline); 0 = neither measurement was high, 1 = either measurement was high, 2 = both measurements were high.

ated with aging phenotypes at the 10-year follow-up in the sex- and age-adjusted analyses (Table 2). After further adjustment for potential confounders, participants with a high interleukin-6 level at baseline were significantly less likely than those with a low interleukin-6 level to achieve successful aging (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.35–0.59) and

were at increased risk of a cardiovascular disease event (OR 1.76, 95% CI 1.21–2.55) or death from a noncardiovascular cause (OR 2.64, 95% CI 1.53–4.55) over the 10-year follow-up period (Figure 2). Participants who had a high interleukin-6 level once or twice over the 5-year exposure period were less likely to achieve successful aging than those who never had a high



**Figure 2: Multivariable logistic regression of associations between interleukin-6 (IL-6) levels at baseline (A) and over a 5-year exposure period (B) and subsequent aging phenotypes at 10-year follow-up.** Aging phenotypes were: successful aging (v. normal aging, cardiovascular disease [CVD] event and non-CVD death phenotypes combined), total  $n = 3044$ ; CVD event (v. successful and normal aging phenotypes combined), total  $n = 2897$  (excludes 147 participants who died of non-CVD causes); and non-CVD death (v. successful and normal aging phenotypes combined), total  $n = 2723$  (excludes 321 participants who had fatal or nonfatal CVD event). For model A, IL-6 levels were separated into 3 categories: low ( $\leq 1.0$  ng/L), intermediate (1.1–2.0 ng/L) and high ( $> 2.0$  ng/L). For model B, IL-6 was measured twice (5 yr before baseline and at baseline); 0 = neither measurement was high, 1 = either measurement was high, 2 = both measurements were high. Odds ratios (ORs) were adjusted for sex, age, socioeconomic status, smoking status, physical activity, acute inflammation and use of anti-inflammatory drugs; values greater than 1.0 indicate an increased likelihood of the outcome. CI = confidence interval, ref = reference group.

level during the exposure period (OR for having a high level once 0.66, 95% CI 0.53–0.82; OR for having a high level twice 0.53, 95% CI 0.38–0.74;  $p_{\text{trend}} < 0.001$ ) (Figure 2). Having a high interleukin-6 level twice over the 5-year exposure period was also associated with an increased risk of cardiovascular disease (OR 1.64, 95% CI 1.15–2.33;  $p_{\text{trend}} = 0.002$ ) and death from a noncardiovascular cause (OR 2.43, 95% CI 1.56–3.80;  $p_{\text{trend}} < 0.001$ ). When we replaced interleukin-6 by C-reactive protein in the regression model, we observed similar significant associations with aging phenotypes (Appendix 4, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1)).

When we examined the individual components of successful aging, we found that high interleukin-6 levels at baseline were associated with lower odds of good cardiovascular, respiratory and musculoskeletal functioning and good mental well-being, as well as lower odds of remaining free of diabetes and disability (Table 3). When inflammation was assessed over the 5-year exposure period, we observed that having a high interleukin-6 level twice over the exposure period was associated with lower odds of good respiratory and musculoskeletal functioning and lower odds of remaining free of diabetes (Table 3).

Repeated analyses with multinomial regression to examine potential competing risk bias gave findings similar to those in the main analysis, which suggested that competing risk bias was unlikely (Appendix 5, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1)). In further sensitivity analyses, the results did not materially change after we excluded obese participants (body mass index  $\geq 30$ ), those taking anti-inflammatory medications or those with acute inflammation (C-reactive protein  $> 10$  mg/L) (Appendix 6, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.122072/-/DC1)). The OR for the association between inflammation and noncardiovascular death among the 5353 participants with complete data on inflammation and cause of death was largely similar to the OR among the 3044 participants included in the main analyses. Furthermore, when we used multiple imputation to deal with missing data on inflammation and covariates, we noted associations similar to those reported in the main analyses. Finally, the net reclassification improvement calculations showed that information from 2 measurements of inflammation improved the risk prediction for successful aging by 23.6%, for cardiovascular events by 15.4% and for noncardiovascular death by 22.1% (Appendix 7, avail-

**Table 3:** Association between interleukin-6 levels at baseline and over the 5-year exposure period and individual components of successful aging\* at 10-year follow-up among 2576 participants†

Variable	Component of successful aging; adjusted OR‡ (95% CI)							
	Good cardiovascular functioning	Absence of diabetes	Good respiratory functioning	Good musculoskeletal functioning	Good cognitive functioning	Good mental well-being	Absence of cancer	Absence of disability
IL-6 levels§ at baseline								
Low (ref)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	0.93 (0.73–1.19)	0.52 (0.37–0.75)	0.80 (0.60–1.07)	0.77 (0.59–1.00)	1.03 (0.79–1.36)	0.71 (0.49–1.04)	0.62 (0.44–0.89)	0.71 (0.53–0.96)
High	0.74 (0.56–0.98)	0.35 (0.24–0.51)	0.53 (0.39–0.72)	0.62 (0.45–0.83)	0.93 (0.68–1.28)	0.56 (0.37–0.86)	0.79 (0.52–1.20)	0.62 (0.44–0.86)
$p_{\text{trend}}$ value	0.04	< 0.001	< 0.001	0.001	0.7	0.01	0.3	< 0.001
No. of times IL-6 level was high over 5-yr exposure period¶								
0 (ref)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	0.72 (0.58–0.90)	0.66 (0.51–0.87)	0.71 (0.55–0.92)	0.86 (0.68–1.09)	0.79 (0.62–1.01)	0.80 (0.58–1.11)	1.15 (0.83–1.59)	0.89 (0.69–1.15)
2	0.76 (0.55–1.06)	0.44 (0.31–0.62)	0.41 (0.30–0.58)	0.67 (0.49–0.93)	0.79 (0.56–1.12)	0.71 (0.46–1.09)	0.82 (0.54–1.23)	0.80 (0.57–1.13)
$p_{\text{trend}}$ value	0.01	< 0.001	< 0.001	0.02	0.06	0.07	0.7	< 0.001

Note: CI = confidence interval, OR = odds ratio.

\*Free of major chronic disease and with optimal physical, mental and cognitive functioning.

†Participants who had a fatal or nonfatal cardiovascular disease (CVD) event and those who died from a non-CVD cause ( $n = 468$ ) were excluded from these analyses.

‡Adjusted for sex, age, socioeconomic status, smoking status, physical activity, acute inflammation and use of anti-inflammatory drugs.

§Low =  $\leq 1.0$  ng/L, intermediate = 1.1–2.0 ng/L, high =  $> 2.0$  ng/L.

¶Interleukin-6 was measured twice (5 yr before baseline and at baseline); 0 = neither measurement was high, 1 = either measurement was high, 2 = both measurements were high.

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## Interpretation

We showed that having chronically high levels of interleukin-6 halved the odds of successful aging 10 years later and was associated with increased odds of future cardiovascular disease and death from noncardiovascular causes in a dose–response fashion. These associations were independent of socioeconomic factors, health behaviours (smoking, physical activity), conditions such as obesity, acute inflammation and the use of anti-inflammatory drugs.

Most previous studies investigated the impact of inflammation on cardiovascular and mortality outcomes based on only a single measurement of inflammation.<sup>4</sup> A recent collaborative meta-analysis suggested that prolonged increases in interleukin-6 levels were associated with an increased risk of coronary artery disease.<sup>10</sup> In that report, the long-term average impact of interleukin-6 was estimated from a single measure of the inflammatory marker using a “regression dilution ratio” method. Our use of repeated measures of interleukin-6 confirmed this finding.

Three studies reported on an association between change in interleukin-6 levels and age-related health outcomes. Two studies, involving 860<sup>21</sup> and 736<sup>22</sup> older adults, showed that short-term (3-yr) and long-term (9-yr) increases in interleukin-6 were associated with an increased 3-year risk of overall mortality. A further study based on the Cardiovascular Health Study All Stars study ( $n = 840$ )<sup>23</sup> showed that the 9-year increase in interleukin-6 was also associated with an increased risk of cardiovascular disease. Our results on the associations between inflammation, cardiovascular events and death from noncardiovascular causes are concordant with those reported in the literature. However, our results also show that measuring chronic inflammation twice may be a better predictor of future cardiovascular disease and noncardiovascular death than measuring inflammation only once.

We found that chronic inflammation characterized by a high interleukin-6 level ( $> 2.0$  ng/L) measured twice over the 5-year exposure period nearly halved the odds of successful aging after 10 years of follow-up compared with maintaining a low level of interleukin-6 ( $< 1.0$  ng/L twice over the exposure period). Our study showed that high interleukin-6 levels at baseline were inversely associated with most of the individual components that characterize successful aging: good cardiovascular, respiratory and musculoskeletal functioning, good mental well-being,

and the absence of diabetes and disability. Exceptions were components related to good cognitive function and the absence of cancer. Regarding cognition, a more robust association with inflammation was expected according to the available epidemiologic literature, which supported an association between inflammation and cognitive decline.<sup>5</sup> In contrast, the nonsignificant association between inflammation and cancer reported in our study is in accordance with the results of the British Women’s Heart and Health Study.<sup>24</sup> It showed that, in a cohort of 4286 women aged 60–79 years, elevated interleukin-6 concentrations were similarly associated with an increased risk of death among older women with and without cancer, which suggested that these inflammatory markers were indicators of nonmalignant comorbidities rather than cancer itself.<sup>24</sup>

Our results also suggest that maintaining a low interleukin-6 level may facilitate successful aging by reducing the likelihood of impaired respiratory and musculoskeletal functioning and increasing the likelihood of remaining free of diabetes.

## Limitations

This study has some important limitations. First, because our study cohort was comprised exclusively of middle-aged, London-based civil servants at baseline, findings may have limited generalizability.<sup>15</sup>

Second, we restricted analyses to participants who had complete data on aging outcomes and inflammatory markers, which constituted only 53% of the 5706 participants at baseline (Figure 1). However, comparable results observed in supplementary analyses — one in which we included all participants for whom mortality records were available, and the other in which we used multiple imputation methods to deal with missing data — suggest that a major bias due to sample selection was unlikely an explanation for our results.

Third, we used 2 measurements of interleukin-6 over the 5-year exposure period to assess long-term inflammation. Although we showed that the ability to predict aging phenotypes was significantly better when inflammation was assessed twice rather than once, having a high interleukin-6 level at the beginning and end of a 5-year exposure period should not necessarily be regarded as an indicator of chronic inflammation, because repeated short-term inflammatory responses are possible.

Finally, common to other observational studies and despite adjustment for sociodemographic and health behaviour factors, we cannot exclude the possibility that the observed associations between inflammation and aging phenotypes may be explained in part by residual confounding.

## Conclusion

By analyzing aging phenotypes based on validated clinic-based measures and medical records in a large sample with a long follow-up, we were able to show that chronic inflammation, as ascertained by repeat measurements of interleukin-6, was related to a range of unhealthy aging phenotypes and a decreased likelihood of successful aging. Maintaining a low interleukin-6 level may facilitate successful aging by reducing the likelihood of impaired respiratory and musculoskeletal functioning and increasing the likelihood of remaining free of diabetes. If confirmed, these results shed new light on the importance of assessing long-term chronic inflammation in geriatric clinical practice, not only to target individuals at risk of unhealthy aging but also to promote ideal health by managing long-term chronic inflammation.

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