Associations Between Fibrin D-Dimer, Markers of Inflammation, Incident Self-Reported Mobility Limitation, and All-Cause Mortality in Older Men

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OBJECTIVES: To examine the independent relationships between fibrin D-dimer, interleukin 6 (IL-6), C-reactive protein (CRP), and fibrinogen and incident mobility limitation and mortality.

DESIGN: Prospective.

SETTING: General practice in 24 British towns.

PARTICIPANTS: Men aged 60 to 79 without prevalent heart failure followed up for an average of 11.5 years (N = 3,925).

MEASUREMENTS: All-cause mortality (n = 1,286) and self-reported mobility disability obtained at examination in 1998 to 2000 and in a postal questionnaire 3 to 5 years later in 2003.

RESULTS: High D-dimer (top vs lowest tertile: adjusted odds ratio (aOR) = 1.46, 95% confidence interval = 1.02–2.05) and IL-6 (aOR = 1.43, 95% CI = 1.01–2.02) levels (but not CRP or fibrinogen) were associated with greater incident mobility limitation after adjustment for confounders and prevalent disease status. IL-6, CRP, fibrinogen, and D-dimer were significantly associated with total mortality after adjustment for confounders. Only D-dimer and IL-6 predicted total mortality independent of each other and the other biomarkers. The adjusted hazard ratio (aHR) was 1.16 (95% CI = 1.10–1.22) for a standard deviation increase in log D-dimer and 1.10 (95% CI = 1.04–1.18) for a standard deviation increase in log IL-6. D-dimer was independently related to vascular and nonvascular mortality, and IL-6 was independently related to vascular mortality. Risks of mobility limitation and mortality were greatest in those with a combination of high D-dimer and IL-6 levels.

CONCLUSION: D-dimer and IL-6 are associated with risk of mobility limitation and mortality in older men without heart failure. The findings suggest that coagulation leads to functional decline and mortality s that inflammation does not explain. **J Am Geriatr Soc 62:2357–2362, 2014.**

Key words: D-dimer; inflammation; mobility limitation; mortality

Aging is characterized by chronic low-grade inflammation that is involved in the pathophysiology and course of many age-related disorders.[1] Proinflammatory cytokines such as interleukin 6 (IL-6) play a central role in the hepatic production of C-reactive protein (CRP), fibrinogen, and other acute-phase proteins involved in the inflammatory process and may also play a role in the activation of coagulation.[2] Fibrin D-dimer, a marker of on-going fibrin formation and degradation, is the most commonly used clinical assay for the detection of activation of the coagulation system.[3] D-dimer is also an acute-phase reactant whose production stimulates high levels of cytokines such as IL-6 influence.[4] In turn, D-dimer and other fibrin degradation products may also influence inflammatory and acute-phase responses by promoting neutrophil and monocyte activation, inducing the release of IL-6.[5]

High circulating levels of markers of inflammation and coagulation, most notably CRP, IL-6, and D-dimer increase with advancing age[1,6] and have been associated with functional decline, cardiovascular disease (CVD), and total mortality.[7–22] Whether the association between CRP and mobility limitation and mortality reflects upregulation by IL-6 is not well established. Few studies have examined to what extent the inflammatory and coagulation pathways are independently associated with mobility limitation and mortality, although is has been suggested that coagulation pathways have mechanisms independent of inflammation.[13] The association between IL-6, CRP, D-dimer, and

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DOI: 10.1111/jgs.13133

0002-8614/14/$15.00

fibrinogen and incident mobility limitation and all-cause mortality was therefore assessed in men aged 60 to 79, and whether the association between D-dimer and incident mobility limitation and mortality was attributable to IL-6 or CRP (or vice versa) was assessed.

METHODS AND PARTICIPANTS

The British Regional Heart Study is a prospective study of CVD involving 7,735 men aged 40 to 59 selected from one general practice in each of 24 British towns who were screened between 1978 and 1980.[23] The population studied was socioeconomically representative of British men but consisted almost entirely of white Europeans (>99%). In 1998 to 2000, all surviving men, now aged 60 to 79, were invited for a 20-year follow-up examination. The men completed a questionnaire (Q20) that included questions on their medical history and lifestyle. They were requested to fast for a minimum of 6 hours, during which time they were instructed to drink only water and to attend for measurement at a prespecified time between 8:00 a.m. and 6:00 p.m. All men were asked to provide a blood sample. Four thousand two hundred fifty-two men (77% of survivors) attended an examination. Follow-up data using self-reported questionnaires (Q03) were collected in 2003. Four thousand forty men had at least one of the four markers (D-dimer, IL-6, CRP, or fibrinogen) and biochemistry measured. Men with a diagnosis of heart failure (n = 115), who have high disability rates and exceptionally high mortality, were excluded. Heart failure is associated with abnormal hemostasis and inflammation,[24] and individuals with heart failure are likely to be taking anticoagulants and other treatments that might have biased the associations between inflammation, coagulation, mobility, and mortality. After these exclusions, 3,925 men were available for analysis.

Cardiovascular Risk Factor Measurements at the 20-Year Examination (1998–2000)

Details of measurements and classification methods for smoking status, physical activity, body mass index, social class, blood pressure, blood lipids, and glucose have been described.[25–27] CVD included recall of a doctor's diagnosis of myocardial infarction, angina pectoris, stroke, deep vein thrombosis (DVT), or peripheral vascular disease. Plasma D-dimer levels were measured using an enzyme-linked immunosorbent assay (ELISA; Biopool AB, Umeå, Sweden). C-reactive protein was assayed using ultrasensitive nephelometry (Dade Behring, Milton Keynes, UK). IL-6 was assayed using a high-sensitivity ELISA (R & D Systems, Oxford, UK). Fibrinogen was assayed using an automated Clauss assay in a coagulometer (MDA-180, Organon Teknika, Cambridge, UK).

Mobility Limitation

At the 20-year examination (1998–2000) and on the follow-up questionnaire in 2003, the men were asked whether they currently had difficulty (i) going up or down stairs, (ii) bending down or straightening up, (iii) keeping their balance, or (iv) walking one-quarter of a mile on the level on their own as a result of a long-term health problem. Mobility limitation was defined as reporting difficulty in (i) and (iv).[27] Analysis of incident mobility limitation (Table 1) was restricted to the 2,731 men who responded to the 2003 follow-up questionnaire and were free of mobility limitation at the 20-year examination (Figure 1).

Follow-Up

All men have been followed up from initial examination (1978–1980) to December 2010 for all-cause mortality and cardiovascular morbidity,[28] and follow-up has been achieved for 99% of the cohort. In the present analyses, all mortality follow-up was based on follow-up from rescreening in 1998 to 2000 (aged 60–79) and a mean follow-up of 11.5 years (range 10.5–12.5 years). Information on death was collected through the National Health Service registers. Cardiovascular deaths include all those with *International Classification of Diseases, Ninth Revision*, codes 401 to 459.

Statistical Methods

Analyses are based on the division of the distribution of CRP, IL-6, fibrinogen, and D-dimer into equal thirds in all 3,925 men. Cox proportional hazards models were used to assess the multivariate-adjusted relative risk. In the adjustment, smoking (never, long-term ex-smoker (>15 years), recent ex-smoker, current smoker), social class (seven groups), physical activity (four groups), alcohol intake (five groups), preexisting diabetes mellitus (yes/no), CVD (yes/no), respiratory medication (yes/no), self-rated health (poor/fair), and use of antihypertensive drugs (yes/no) were fitted as categorical variables. Body mass index, systolic blood pressure, and high-density lipoprotein cholesterol were fitted as continuous variables. Logistic regression was used to determine adjusted odds ratios of incident mobility limitation (Table 1).

RESULTS

During a mean follow-up of 11.5 years, there were 1,286 deaths from all causes (497 CVD, 786 non-CVD, 3 unknown) in the 3,925 men with no diagnosed heart failure.

C-reactive protein was significantly correlated with IL-6 (correlation coefficient (r) = 0.57), fibrinogen (r = 0.48), and D-dimer (r = 0.33). Table 1 shows the association between the four markers and adjusted odds of incident mobility limitation (n = 288). D-dimer and IL-6, but not CRP or fibrinogen, were significantly associated with greater odds of incident mobility limitation after adjustment for lifestyle characteristics and disease status (Model 1). The association between D-dimer and incident mobility limitation remained significant after adjustment for IL-6 and was strengthened after exclusion of men with prevalent CVD or those who reported a diagnosis of CVD at follow-up (top vs bottom tertile: adjusted odds ratio = 1.63, 95% CI = 1.03–2.58). Adjustment for D-dimer slightly attenuated the association between IL-6 and mobility limitation and the association was no longer significant. The combined effect of D-dimer and IL-6 was examined. Those with high IL-6 and D-dimer had much higher odds of incident mobility limitation than having just one high marker (Table 1).

Table 1. Associations Between Tertiles of D-Dimer, C-Reactive Protein (CRP), Interleukin (IL)-6, and Fibrinogen and Incident Mobility Limitation (n = 288 cases) and Adjusted Odds Ratio of Incident Mobility Limitation in 2,731 Men Who Reported No Prevalent Mobility Limitation and No Prevalent Heart Failure

			Age Adjusted	Model 1	Model 2
Tertile	N	Incident Mobility, %	Odds Ratio of Incident Mobility Limitation (95% Confidence Interval)		
D-dimer, ng/mL					
Low (<58)	1,028	7.1	1.00	1.00	1.00
Middle (58–103)	947	10.8	1.35 (0.98–1.86)	1.25 (0.88–1.74)	1.23 (0.88–1.73)
Upper (>104)	749	15.1	1.76 (1.27–2.45)	1.46 (1.03–2.06)	1.42 (1.00–2.01)
Test for trend			$P = .006$	$P = .03$	$P = .05$
CRP, mg/L					
Low (<1.03)	1,019	6.5	1.00	1.00	
Middle (1.03–2.57)	926	11.1	1.82 (1.32–2.51)	1.31 (0.94–1.85)	
Upper (>2.58)	763	13.6	2.06 (1.48–2.85)	1.23 (0.86–1.77)	
Test for trend			$P < .001$	$P = .31$	
IL-6, pg/mL					
Low (<1.77)	1,027	6.7	1.00	1.00	1.00
Middle (1.78–2.91)	919	10.8	1.45 (1.05–2.01)	1.21 (0.87–1.72)	1.19 (0.84–1.67)
Upper (>2.92)	759	15.5	2.20 (1.60–3.02)	1.43 (1.01–2.02)	1.35 (0.95–1.92)
Test for trend			$P < .001$	$P = .04$	$P = .10$
Fibrinogen (g/L)					
Low (<2.93)	989	7.7	1.00	1.00	
Middle (2.93–3.43)	941	11.1	1.34 (0.98–1.84)	1.21 (0.87–1.68)	
Upper (>3.44)	794	13.6	1.63 (1.19–2.24)	1.17 (0.83–1.64)	
Test for trend			$P = .002$	$P = .91$	
Composite index: IL6 and D-dimer					
0 (both low)	491	5.5	1.00	1.00	
1 (middle tertile of IL6 or D-dimer)	649	8.2	1.38 (0.86–2.24)	1.19 (0.73–1.96)	
2 (middle tertile of both)	347	12.91	1.52 (0.90–2.59)	1.26 (0.72–2.18)	
3 (high IL-6 only)	469	12.6	2.10 (1.30–3.39)	1.32 (0.80–2.20)	
4 (high D-dimer only)	455	11.7	1.69 (1.03–2.79)	1.33 (0.79–2.23)	
4 (both markers high)	287	20.6	3.20 (1.95–5.22)	1.88 (1.11–3.19)	
Test for trend			$P < .001$	$P = .01$	

Missing data: D-dimer, n = 7; CRP, n = 23; IL-6, n = 26; fibrinogen, n = 7.

Model 1 adjusted for age, smoking, physical activity, alcohol intake, social class, body mass index, diabetes mellitus, history of cardiovascular disease or cancer, respiratory medication, self-rated health, use of antihypertensive drugs, and systolic blood pressure.

Model 2: For IL-6, adjustments were made for factors in Model 1 and for D-dimer. For D-dimer, adjustments were made for factors in Model 1 and for IL-6.

Test for trend across the groups.

Table 2 shows the adjusted hazard ratio for total, CVD, and non-CVD mortality for a 1-standard deviation increment in CRP, IL-6, and D-dimer, with stepwise adjustment for the biomarkers. CRP, IL-6, and D-dimer were significantly associated with total, CVD, and non-CVD mortality after adjustment for lifestyle characteristics and disease status. These associations remained significant even after exclusion of men with prevalent CVD or cancer (n = 1,246) (data not shown). The association between CRP and CVD mortality was attenuated when adjustment was made for IL-6. IL-6 and D-dimer levels were associated with total, CVD, and non-CVD mortality independent of CRP. D-dimer emerged as the strongest predictor of total, CVD, and non-CVD mortality when all three markers (IL-6, CRP, D-dimer) were included in the model. Fibrinogen was significantly associated with total, CVD, and non-CVD mortality after adjustment for lifestyle characteristics and disease status, but these associations were attenuated after adjustment for CRP (data not shown).

The joint effect of D-dimer and IL-6 on total mortality was also examined. High D-dimer and IL-6 levels conferred by far the highest risk of mortality. Compared to those with low D-dimer and low IL-6, the adjusted relative risk of mortality for having high IL-6 alone was 1.31 (95% CI = 1.02–1.68), high D-dimer alone was 1.36 (95% CI = 1.07–1.73), and having high IL-6 and D-dimer was 2.07 (95% CI = 1.63–2.64).

DISCUSSION

This large population study of British men aged 60 to 79 confirmed the findings of previous prospective studies that fibrin D-dimer and IL-6 are associated with incident mobility limitation[11–16] and total mortality[16–22] independent of lifestyle characteristics and established cardiovascular risk factors. These findings add to the limited literature on the prospective associations between D-dimer and total and nonvascular mortality and extend those of previous studies on D-dimer, CRP, IL-6, and fibrinogen and mobil-

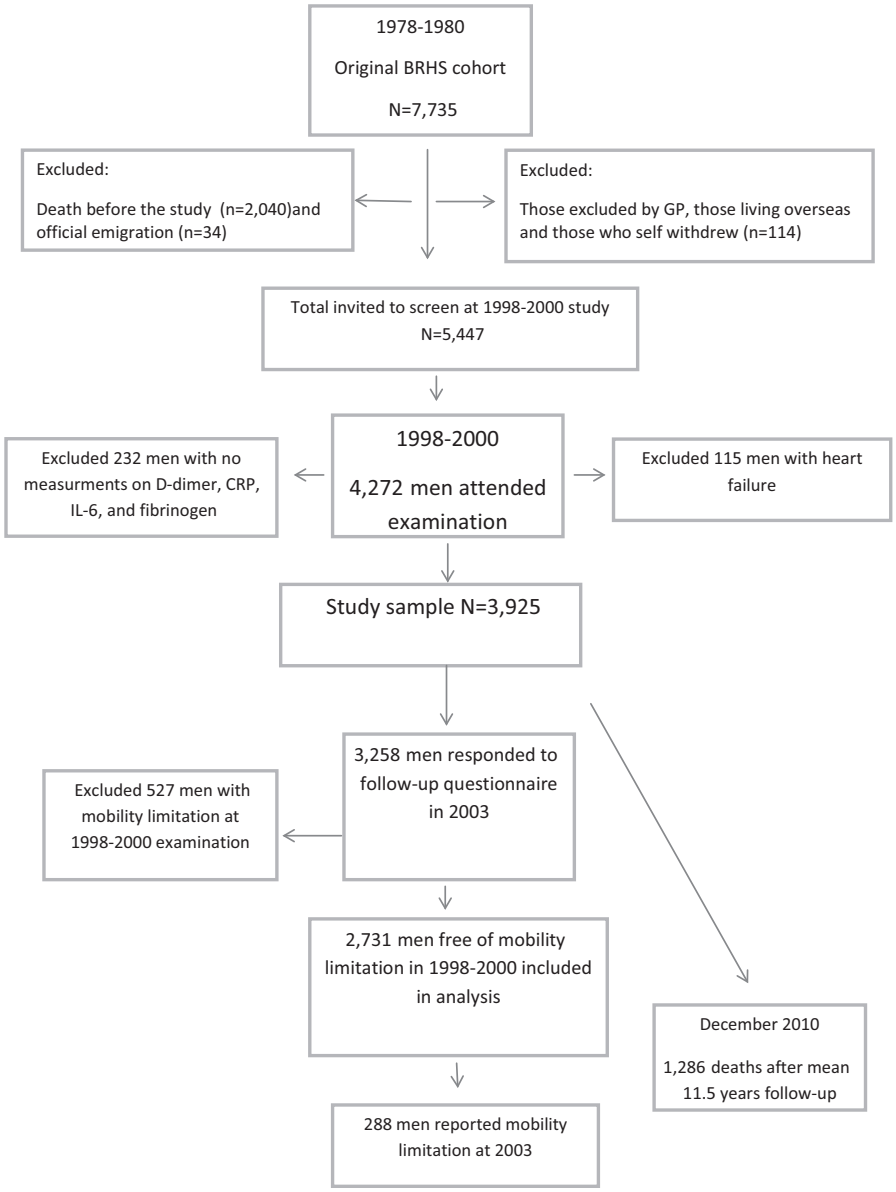

Figure 1. Flowchart displaying the study cohort and participants included in the analysis of mobility limitation and all-cause mortality. BRHS = British Regional Heart Study; GP = general practitioner; CRP = c-reactive protein; IL-6 = interleukin 6.

ity limitation and mortality by comparing all these markers in the same study and assessing their independent relationships.

D-Dimer Levels, Inflammation, and Mobility Limitation

IL-6, but not CRP or fibrinogen, was associated with mobility limitation independent of lifestyle characteristics and disease status. Weaker associations between CRP and mobility limitation have also been reported in other studies.[12,15] Although a number of studies have reported an association between D-dimer, inflammation (in particular IL-6 levels), and incident mobility limitation in the general population,[12,13,16] few have assessed the independence and the interaction of these factors. Chronic inflammation has been proposed as a biological mechanism underlying age-associated functional decline. D-dimer has been shown to stimulate production of IL-6 and other inflammatory mediators that have been directly associated with loss of muscle mass and strength, which leads to mobility limitation, but the association between D-dimer and mobility limitation was independent of IL-6 in multivariate analysis, although activation of coagulation (D-dimer) and inflammation (IL-6) was associated with a much greater risk of mobility limitation than high D-dimer levels alone. This finding suggests independent effects of coagulation on mobility function and of an interaction between coagulation and the inflammation system on mobility function. Although the mechanism by which D-dimer may directly influence mobility limitation is not clear, D-dimer may have a direct influence on mobility limitation by modulating the function of immunocytes to produce cytokines and other mediators with roles in cell migration, vascular remodeling, and endothelial cell activation.[13] D-dimer may also be an important component of age-related

Table 2. Mortality Associated with a 1-Standard Deviation (SD) Increase in Log C-Reactive Protein (CRP), Interleukin (IL)-6, and D-Dimer

	Model 1	Model 2	Model 3
Mortality	**Adjusted Hazard Ratio (95% Confidence Interval)**		
Total			
Log CRP	1.17 (1.09–1.25) <.001	1.09 (1.02–1.17) .01	1.07 (1.00–1.14) .08
Log IL-6	1.18 (1.12–1.25) <.001	1.14 (1.06–1.21) <.001	1.10 (1.04–1.18) .006
Log D-dimer	1.20 (1.15–1.26) <.001	1.17 (1.11–1.23) <.001	1.16 (1.10–1.22) <.001
CVD			
Log CRP	1.21 (1.11–1.32) <.001	1.09 (0.98–1.22) .11	1.06 (0.95–1.18) .36
Log IL-6	1.25 (1.14–1.37) <.001	1.19 (1.07–1.32) .003	1.14 (1.02–1.26) .04
Log D-dimer	1.30 (1.19–1.41) <.001	1.27 (1.17–1.37) <.001	1.24 (1.15–1.35) <.001
Non CVD			
Log CRP	1.14 (1.07–1.22) <.001	1.09 (1.001–1.19) .04	1.07 (0.98–1.17) .12
Log IL-6	1.15 (1.08–1.23) <.001	1.13 (1.01–1.26) .03	1.08 (0.99–1.19) 0.07
Log D-dimer	1.14 (1.07–1.22) <.001	1.12 (1.03–1.21) .004	1.11 (1.04–1.18) .008

1-SD increase in log IL-6 = 0.67, log CRP = 1.11, log D-dimer = 0.84, fibrinogen = 0.73.

Model 1 adjusted for age, smoking, physical activity, alcohol intake, social class, body mass index, diabetes mellitus, history of cardiovascular disease (CVD) or cancer, self- rated health, use of antihypertensive drugs, systolic blood pressure, high-density lipoprotein cholesterol, and forced expiratory volume in 1 second.

Model 2: Adjusted for factors in Model 1and CRP. For CRP, adjustment was made for IL-6.

Model 3: Adjusted for factors in Model 1 and all three biomarkers (CRP, IL-6, D-dimer).

physiological dysregulation leading to frailty and subsequent mortality,[29] although this remains speculative.

Inflammation, D-Dimer Levels, and Mortality

Inflammatory markers, including CRP, IL-6, and fibrinogen, have been associated with mortality in numerous population studies.[7,8,17–22] Only IL-6 emerged as an independent predictor of mortality when other inflammatory markers were taken into account. The current findings that the association between CRP and CVD mortality was attenuated after adjustment for IL-6 support the suggestion that IL-6 may play an important role in mediating the associations between downstream inflammatory markers such as CRP and CVD.[30] Fibrinogen is an acute-phase reactant protein that rises with tissue inflammation and is a vital part of the common pathway of the coagulation process, although fibrinogen was not related to vascular or nonvascular mortality after adjustment for CRP, as seen in other studies.[20] Fewer studies have examined the association between D-dimer and total and nonvascular mortality in the general population. The current study found a strong association between D-dimer and total, CVD, and non-CVD mortality that was independent of inflammation, consistent with other studies.[17–19]

STRENGTHS AND LIMITATIONS

Strengths and limitations of this study require consideration. The study population was socially representative of the United Kingdom, and follow-up rates in the British Regional Heart Study are exceptionally high. This study is based on a cohort of older (60–79) men, and the results need further confirmation in similar study populations and in middle-aged populations and women. Because mobility outcome is based on survivors who responded to the follow-up questionnaire 4 years later, survival bias may have weakened the true association between coagulation, inflammation, and mobility limitation.

CONCLUSION

Inflammation and coagulation are associated with mobility limitation and mortality. The findings suggest that activated coagulation leads to functional decline and death that inflammation does not explain. If so, future studies of new oral anticoagulants (which reduce coagulation activation and D-dimer) in older persons (e.g., with atrial fibrillation) might reduce the risk of mobility limitation and vascular morbidity and mortality.

ACKNOWLEDGMENTS

The British Regional Heart Study is a British Heart Foundation (BHF) research group and receives support from BHF Programme Grant RG/08/013/25942. The funders had no role in the design or conduct of the study; collection, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Wannamethee: concept and design, data analysis, drafting the manuscript. Whincup, Lowe: data interpretation. Papacosta: data analysis. Lennon, Whincup: data acquisition. All authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Sponsor's Role: None.

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