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Elevated plasma fibrinogen, psychological distress, antidepressant use, and hospitalization with depression: Two large population-based studies

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Fibrinogen;
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Summary
Objectives: Low-grade systemic inflammation may contribute to the development of depression. We tested the hypothesis that elevated plasma levels of the inflammatory marker fibrinogen are associated with psychological distress, use of antidepressant medication, and with hospitalization with depression in the general population.
Methods: We examined 73,367 20—100 year old men and women from two large population-based studies, the Copenhagen General Population Study and the Copenhagen City Heart Study. We measured plasma fibrinogen and recorded symptoms of psychological distress, use of antidepressant medication, and hospitalization with depression in both cross-sectional and prospective studies.
Results: In cross-sectional analyses, a stepwise increase in fibrinogen percentile categories was associated with a stepwise increase in risk of psychological distress, use of antidepressant medication, and hospitalization with depression (p-trend 2×10^{-11} to 5×10^{-95}). Furthermore, when different classes of antidepressant medication were examined, a stepwise increase in fibrinogen percentile categories was associated with a stepwise increase in risk of use of Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants (p-trend 7×10^{-18} and 6×10^{-7}, respectively). In prospective analyses, stepwise increasing fibrinogen percentile categories also associated with stepwise increasing risk of hospitalization with depression (p-trend = 7×10^{-6}): age and gender adjusted hazard ratios were 1.13 (95% confidence interval 0.70—1.83) for the 25.1—50th percentiles, 1.53 (0.97—2.42) for the 50.1—75th percentiles, 1.82 (1.11—2.97) for the 75.1—90th percentiles, 2.10 (1.12—3.95) for the 90.1—95th percentiles, and 3.23 (1.79—5.85) for the >95th percentiles, versus the 0—25th percentiles.

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Conclusion: Elevated levels of fibrinogen were associated with psychological distress, use of antidepressant medication, and with hospitalization with depression in 73,367 individuals from the general population, in cross-sectional studies and in prospective studies for hospitalization with depression.

1. Introduction

With a prevalence up to 10%, depression is the most frequent psychiatric disease in the Western World (World Health and Organisation, 2005). While the exact disease mechanism is unknown, low-grade inflammation possibly plays a role in the development of depression, and previous studies have shown an association between depression and elevated inflammatory markers such as cytokines and acute phase proteins (Maes et al., 1997; Howren et al., 2009; Dowlati et al., 2010).

Fibrinogen is an important acute phase protein and plasma levels increase due to inflammation (de Moerloose et al., 2010). The acute increase in plasma fibrinogen levels after an inflammatory stimulus is approximately 200% within 3 weeks (Gabay and Kushner, 1999). Furthermore, baseline plasma fibrinogen levels are strongly positively associated with other markers of chronic inflammation such as plasma C-reactive protein and blood leucocytes (Kaptoge et al., 2007). Previous studies have examined the association between fibrinogen and psychological distress and depression with conflicting results (Maes et al., 1997; von Kanël et al., 2001; Kop et al., 2002; Steptoe et al., 2003; Panagiotakos et al., 2004; Doulalas et al., 2006; Lahlou-Laforet et al., 2006; Matthews et al., 2007; Whooley et al., 2007; Nabi et al., 2008; Baune et al., 2010; Goldman-Mellor et al., 2010; Kop et al., 2010, Wium-Andersen et al., in press). First, two population-based studies with 1300 and 6400 participants investigated the association between elevated fibrinogen levels and psychological distress: one reported an association (Goldman-Mellor et al., 2010) while the other did not (Nabi et al., 2008). Second, Matthews et al. found an association between elevated fibrinogen levels and depressive symptoms in a population-based sample of 3300 women (Matthews et al., 2007), which is consistent with the findings of others (Maes et al., 1997; Panagiotakos et al., 2004; Kop et al., 2010; Wium-Andersen et al., in press); however, yet other studies including 200—4300 participants showed no association between fibrinogen and depression (Kop et al., 2002; Steptoe et al., 2003; Doulalas et al., 2006; Lahlou-Laforet et al., 2006). Finally, two other studies have findings in the opposite direction (Whooley et al., 2007; Baune et al., 2010), with lower levels of fibrinogen being associated with depression. Thus, due to these ambiguous results, the association between elevated levels of fibrinogen and psychological distress and depression remains unclear.

We tested the hypothesis that elevated plasma levels of fibrinogen are associated with symptoms of psychological distress, use of antidepressant medication, and with hospitalization with depression in the general population; we focused on extreme levels of fibrinogen as done previously for other biomarkers in cardiovascular disease (Nordestgaard et al., 2007; Kamstrup et al., 2008), as individuals with the extreme high levels may be those particularly at risk, and thus extreme levels may clinically be most important. To examine this we measured fibrinogen in 73,367 participants from two large independent general population studies, the Copenhagen General Population Study and the Copenhagen City Heart Study with up to 20 years of follow-up, and corrected results for regression dilution bias. To ascertain symptoms of psychological distress we used responses to questions concerning of not having accomplished much and of wanting to give up. To ascertain use of antidepressant medication we used two independent sources of information: use of self-reported as well as prescription antidepressant medication. Finally, to ascertain depression we used hospitalization with depression.

2. Methods

This study was approved by Herlev Hospital and a Danish ethical committee (KF-100.2039/91 and H-KF-01-144/01). Written consent was obtained from all participants.

2.1. Participants

We included 73,367 men and women from two independent prospective studies, the Copenhagen General Population Study (n = 62,883) and the Copenhagen City Heart Study 1991—1994 examination and 2001—2003 examination (n = 10,484). Participants were 20—100 years old and were randomly selected from the Danish Central Person Register to represent the general population, and no participant appeared in more than one study. All participants were white and of Danish descent. On the day of attendance, participants filled in a questionnaire which was reviewed together with an investigator. Furthermore, all participants had a physical examination performed, and had blood samples drawn for biochemical analysis.

2.2. Fibrinogen measurement

For participants in the Copenhagen City Heart Study 1991—1994 examination, fibrinogen was measured after blood sampling using a calorimetric method (Boehringer Mannheim, Mannheim, Germany). For the participants in the Copenhagen City Heart Study 2001—2003 examination and the Copenhagen General Population Study, fibrinogen was measured using a turbidimetry method (Instrumentation Laboratory, Milano, Italy). Plasma fibrinogen distributions with means and standard deviations for each study are shown in the Supplementary Data (Supplementary Fig. 1). All measurements were done by laboratory technicians who were unaware of the disease status of the participants. Measurements were included in daily internal and monthly external routine quality control programs to ensure precision and accuracy of the analyses.