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Full-length Article

Social isolation, loneliness, and inflammation: A multi-cohort investigation in early and mid-adulthood

Timothy Matthews [a,*,1], Line Jee Hartmann Rasmussen [b,c,1], Antony Ambler [d], Andrea Danese [d,e], Jesper Eugen-Olsen [c,f], Daisy Fancourt [g], Helen L. Fisher [d,h], Kasper Karmark Iversen [i,j,k], Martin Schultz [i], Karen Sugden [b], Benjamin Williams [b], Avshalom Caspi [b,d], Terrie E. Moffitt [b,d]

[a] School of Human Sciences, Faculty of Education, Health and Human Sciences, University of Greenwich, London, United Kingdom
[b] Department of Psychology and Neuroscience, Duke University, Durham, NC, USA
[c] Department of Clinical Research, Copenhagen University Hospital Amager and Hvidovre, Hvidovre, Denmark
[d] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[e] National and Specialist CAMHS Trauma and Anxiety Clinic, South London and Maudsley NHS Foundation Trust, London, United Kingdom
[f] ViroGates A/S, Birkerød, Denmark
[g] Department of Behavioural Science and Health, University College London, United Kingdom
[h] ESRC Centre for Society and Mental Health, King's College London, London, United Kingdom
[i] Department of Emergency Medicine, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark
[j] Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark
[k] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

Social isolation and loneliness have been associated with poor health and increased risk for mortality, and inflammation might explain this link. We used data from the Danish TRIAGE Study of acutely admitted medical patients (N = 6,144, mean age 60 years), and from two population-representative birth cohorts: the New Zealand Dunedin Longitudinal Study (N = 881, age 45) and the UK Environmental Risk (E-Risk) Longitudinal Twin Study (N = 1448, age 18), to investigate associations of social isolation with three markers of systemic inflammation: C-reactive protein (CRP), interleukin-6 (IL-6), and a newer inflammation marker, soluble urokinase plasminogen activator receptor (suPAR), which is thought to index systemic chronic inflammation. In the TRIAGE Study, socially isolated patients (those living alone) had significantly higher median levels of suPAR (but not CRP or IL-6) compared with patients not living by themselves. Social isolation prospectively measured in childhood was longitudinally associated with higher CRP, IL-6, and suPAR levels in adulthood (at age 45 in the Dunedin Study and age 18 in the E-Risk Study), but only suPAR remained associated after controlling for covariates. Dunedin Study participants who reported loneliness at age 38 or age 45 had elevated suPAR at age 45. In contrast, E-Risk Study participants reporting loneliness at age 18 did not show any elevated markers of inflammation. In conclusion, social isolation was robustly associated with increased inflammation in adulthood, both in medical patients and in the general population. It was associated in particular with systemic chronic inflammation, evident from the consistently stronger associations with suPAR than other inflammation biomarkers.

1. Introduction

The importance of social relationships for health and longevity is supported by a large and growing body of evidence (Umberson and Montez, 2010), such that the Surgeon General of the United States has declared social connection to be a public health issue of significant urgency (US Department of Health and Human Services, 2023). According to a *meta*-analysis, social isolation, loneliness, and living alone are each associated with a 25–30 % increase in risk for mortality (Holt-Lunstad et al., 2015). Numerous mechanisms for this association have been

* Corresponding author.
E-mail address: t.matthews@greenwich.ac.uk (T. Matthews).
[1] TM and LJHR are joint first authors.

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proposed, ranging from maladaptive health-related behaviours (Kobayashi and Steptoe, 2018), to increased blood pressure (Hawkley et al., 2010) and impaired sleep quality (Matthews et al., 2017).

Another pathway through which deficits in social relationships could influence health is inflammation. According to a hypothesis based on evolutionary theory (Cacioppo et al., 2006), *loneliness* – a negative emotional state arising with perceived shortcomings in social relationships – is an adaptive response to social disconnection that prepares individuals to face an unsafe environment without protection from kith and kin. Based on this premise, it is hypothesised that loneliness is accompanied by changes in immune functioning that would bolster an individual's ability to fight infection in event of wounding. Consistent with this, individuals high in feelings of loneliness exhibit a pattern of pro-inflammatory changes in gene expression (Cole et al., 2007).

The existing literature on social connection and inflammation has yielded mixed findings, in part likely reflecting differences in methodology. Most studies have used data from community-based samples or experimental conditions involving healthy adults. However, there may be at-risk groups in the population for whom the health risks of social isolation are particularly salient. In the case of inflammation, patients receiving medical care may be one such group, and thus there is merit in examining social deficits in clinical samples as well as population-based cohorts. If social isolation is associated with greater inflammation among people presenting for medical treatment, the clinical importance of this risk factor may be reinforced, as it may have implications for patient outcomes.

A second limitation is that previous studies have often conflated social isolation and loneliness, or only examined one of the two. The domain of social connection encompasses a range of constructs that concern different aspects of individuals' relationships, including quantity, quality, diversity, supportiveness (Holt-Lunstad, 2018). Social isolation and loneliness are two phenomena which frequently co-occur but which refer to specific, distinct aspects of social connection. Specifically, social isolation refers to the circumstance of having limited or minimal social connection with others, whereas loneliness is a subjective, emotional state that reflects individuals' appraisals of their social relationships. Hence, not all isolated individuals are lonely, nor are all lonely individuals isolated (Matthews et al., 2016). Of the two, it is not clear which is the 'active ingredient' in predicting inflammatory outcomes. Studies focusing specifically on loneliness have yielded mixed results (Balter et al., 2019; Hackett et al., 2012; Mezuk et al., 2016; Nersesian et al., 2018; Pavela, Kim, and Salvy, 2018; Shiovitz-Ezra and Parag, 2019; Van Bogart et al., 2022), with most finding null associations. Those studies that have examined both isolation and loneliness in parallel (Shankar et al., 2011) suggest that objective social isolation, rather than loneliness, is the more relevant risk factor for inflammation outcomes. Furthermore, research comparing different indicators of social isolation, such as cohabiting status and social engagement, have found that these are consistently associated with markers of inflammation (Walker, Ploubidis, and Fancourt, 2019).

A third limitation, however, is that studies examining both social isolation and loneliness in the same samples have tended to have cross-sectional designs and cannot address the possibility that individuals suffering from elevated inflammation may, as a result of underlying illness, be restricted from engaging in social activities. Moreover, even if it is hypothesised that social isolation increases susceptibility to inflammation, it is unclear whether this is a transient effect, or if the risk conferred can be detected some years later. If the latter is indeed the case, this would raise the possibility that the developmental period in which social isolation is experienced (e.g., early versus middle adulthood) may be relevant to the risk of inflammation later in life. Prospective cohort studies offer a means of addressing these issues. A small number of longitudinal studies have found that childhood social isolation predicts increased inflammation in adults (Danese et al., 2009; Lacey, Kumari, and Bartley, 2014), but there is limited longitudinal research about childhood loneliness. A further issue still is that loneliness is highly correlated with depression (Matthews et al., 2016), and with lifestyle factors such as smoking (Matthews et al., 2019). Studies that fail to take these into account may yield associations that are confounded.

There are several ways to assess systemic inflammation, each with advantages and disadvantages in their cost, utility, and predictive validity. We recently identified one such marker of systemic inflammation, suPAR (*soluble urokinase plasminogen activator receptor*), as a more reliable measure of chronic inflammation than other, more traditional measures of systemic inflammation used in clinical or research settings, i.e., high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6). Specifically, we found increased suPAR levels in individuals who had been exposed to early life risk factors, such as adverse childhood experiences or specific victimization experiences (Rasmussen et al., 2019, 2020) as well as in individuals who experienced more stressful life events in adulthood (Bourassa et al., 2021), while CRP and IL-6 were not consistently associated with early adverse experiences and stressful life events.

In contrast to CRP and IL-6, both of which are acute-phase reactants and elevated by acute inflammation and infections (Hunter and Jones, 2015; Rhodes, Fürnrohr, and Vyse, 2011), suPAR appears to be less affected by acute conditions (Lyngbæk et al., 2012) and therefore potentially a better measure of chronic systemic inflammation (Rasmussen et al., 2021). The plasma level of suPAR is thought to reflect a person's overall level of immune activity (Rasmussen et al., 2021), and elevated suPAR is observed in a wide range of diseases and pathological conditions (Hayek et al., 2015; Persson et al., 2014; Schaefer et al., 2017; Theilade et al., 2015). Research indicates that suPAR is associated with clinical outcomes independent of CRP and IL-6 (Botha et al., 2015; Rasmussen et al., 2016). If social isolation confers a cumulative effect on health over time via inflammation, suPAR may be a more reliable indicator of the impact on systemic chronic inflammation compared to these other biomarkers.

1.1. Present study

The present study used data from a Danish clinical sample, and two population-representative birth cohorts in the UK and New Zealand (NZ), to investigate the associations of living alone, and measures of social isolation and loneliness with markers of systemic inflammation, including the traditional inflammation markers CRP and IL-6 and the newer inflammation marker suPAR. First, we analysed whether social isolation among unselected acutely admitted medical patients, as measured by living alone, is associated with elevated inflammation in the TRIAGE Study. This allowed us to test whether social isolation and inflammation are connected in a representative, heterogeneous clinical sample of adult patients presenting to a hospital, to attest to the clinical relevance of this association. Second, since "living alone" is an imperfect proxy for lack of social connection, we turned to two well-characterised independent samples, the longitudinal Dunedin and E-Risk birth cohorts, where social isolation and loneliness have been better—and prospectively—measured at different points in the life course, along with numerous covariates of importance. In the case of the E-Risk Study, the twin design further allows for unmeasured genetic and shared environmental sources of confounding to be controlled for. Based on previous literature, we expected that social isolation (rather than loneliness) would be the exposure that is most robustly associated with inflammation, that this association can be observed both cross-sectionally and prospectively, and that the association can be most reliably detected using suPAR in contrast to CRP or IL-6.

2. Methods

2.1. Study populations

2.1.1. The TRIAGE Study

The observational TRIAGE Study investigates various risk-stratification systems that combine biochemical markers with currently available patient data as well as investigating the prognostic value of new and routine biomarkers (Plesner et al., 2015). Patients were consecutively included 24/7 between September 5th, 2013, and December 6th, 2013, from the Emergency Department (ED) at North Zealand University Hospital, Capital Region of Denmark, a 24-h acute care hospital. Patients were included in the Study if they were admitted through the ED, referred to a bed, and had blood samples drawn in the ED (6,163 patients). All patient data were merged in a secure database using each patient's unique civil registration number. Data on demographics, lifestyle, and social aspects were retrieved from the patient record (OPUS Arbejdsplads, version 2.5.0.0, Computer Sciences Corporation) and merged with routine biochemistry results retrieved from the hospital database (LABKA II, version 2.5.0.H2, Computer Sciences Corporation). The Study was conducted according to Danish ethical regulations and was approved by the Danish Data Protection Agency (J. 2007–58-0015). Blood samples were drawn as soon as possible following admission (within 0–60 min) for routine biochemical analyses and for storage in the biobank for subsequent biomarker analysis. Blood for biomarker analyses was spun within 120 min from blood draw for 10 min at 1,800 x g, and serum or plasma drawn off. Samples were stored at −80 °C. This study included patients who had at least one of the inflammatory biomarkers measured (n = 6,144, 99.7 %).

2.1.2. The Dunedin Multidisciplinary Health and Development Cohort (The Dunedin Study)

Participants are members of the Dunedin Study, a longitudinal investigation of health and behaviour in a representative birth cohort. Participants (n = 1037; 91 % of eligible births; 52 % male) were all individuals born between April 1972 and March 1973 in Dunedin, NZ, who were eligible based on residence in the province and who participated in the first assessment at age 3 (Poulton et al., 2015). The cohort represented the full range of socioeconomic status (SES) in the general population of NZ's South Island and as adults matched the NZ National Health and Nutrition Survey on key adult health indicators (e.g., body mass index (BMI), smoking, physical activity, GP visits) and the NZ Census of citizens of the same age on educational attainment (Richmond-Rakerd et al., 2020). The cohort is primarily white (93 %), matching South Island demographics (Poulton et al., 2015). Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently (completed April 2019) 45 years, when 94.1 % (n = 938) of the 997 participants still alive took part. At each assessment, each participant was brought to the research unit for interviews and examinations. The NZ-HDEC (Health and Disability Ethics Committee) approved the Study and written informed consent was obtained from all participants. Venous blood was collected from participants in Serum Separator tubes or EDTA tubes for collection of serum and plasma, respectively. Tubes were spun at 2,500 x g for 10 min, and serum or plasma drawn off. Samples were stored at −80 °C. This study included participants who had at least one of the inflammatory biomarkers measured at age 45 (n = 881, 85.0 %).

2.1.3. Environmental Risk (E-Risk) Longitudinal Twin Study

Participants were members of the E-Risk Longitudinal Twin Study, which tracks the development of a 1994–95 birth cohort of 2,232 British children (Moffitt and E-Risk Study Team, 2002). Briefly, the E-Risk sample was constructed in 1999–2000, when 1,116 families (93 % of those eligible) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprised 56 % monozygotic (MZ) and 44 % dizygotic (DZ) twin pairs; sex was evenly distributed within zygosity (49 % male). The sample represents socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighbourhood-level socioeconomic index (ACORN [A Classification of Residential Neighbourhoods], developed by CACI Inc. for commercial use) (Odgers et al., 2012a, 2012b). Supplementary Fig. 1 (Appendix A) shows E-Risk families' addresses are a near-perfect match to the deciles of the UK's 2015 Lower-layer Super Output Area (LSOA) Index of Multiple Deprivation (IMD) which averages 1,500 residents; approximately 10 % of the cohort fills each of IMD's 10 % bands, a near-perfect match to the population.

Home visits were conducted when participants were aged 5, 7, 10, 12, and most recently, 18 years (93 % participation). At age 18, each twin was interviewed by a different interviewer. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the Study. Parents gave informed consent and twins gave assent between 5 and 12 years and then informed consent at age 18. Whole blood was collected from 82 % (n = 1,700) of the participants. Venous blood was collected from participants in EDTA tubes. Tubes were spun at 2,500 x g for 10 min, and plasma drawn off. Samples were stored at −80 °C. This study included participants who had at least one of the inflammatory biomarkers measured at age 18 (n = 1,448, 64.9 %).

2.2. Measures of social isolation and loneliness

2.2.1. Living alone

In the TRIAGE Study, information on whether a patient was living alone or not was recorded in the patient record at admission and retrieved from the electronic patient record.

2.2.2. Childhood social isolation

Social isolation in adults is typically measured via indicators such as living alone, moving into residential care, or the loss of a spouse. As these are not applicable to children, social isolation in the earlier years of life can be observed through patterns of peer rejection and social withdrawal observed by adults (Caspi et al., 2006; Thompson et al., 2023). In the Dunedin Study, participants' parents and teachers completed the Rutter Child Scales (Elander and Rutter, 1996) when the children were 5, 7, 9, and 11 years old, as previously described. Two items measure peer problems ("tends to do things on his/her own; is rather solitary" and "not much liked by other children"). Scores on these 2 items were averaged across the 4 time periods and by 2 reporters (Cronbach α = 0.77). In the E-Risk Study, social isolation was assessed using six items from the Children's Behavior Checklist and the corresponding items from the Teacher's Report Form (Achenbach 1991a, 1991b), referring to peer rejection and withdrawn behaviours: "complains of loneliness," "doesn't get along with other children/pupils," "feels or complains that no-one loves him/her," "would rather be alone than with others," "not liked by other children [pupils]," and "withdrawn, doesn't get involved with others." Social isolation was assessed when children were aged 5, 7, 10, and 12. At each age, children were categorized as 'low', 'moderate', or 'high' in isolation (Matthews et al., 2015). Individuals were coded as having experienced social isolation in childhood if they were classified high at one or more ages, or moderate at two or more ages.

2.2.3. Loneliness

Loneliness was assessed at ages 38 and 45 in the Dunedin Study, and at age 18 in the E-Risk Study, using four items from the UCLA Loneliness Scale (Russell, 1996): "How often do you feel that you lack companionship?", "How often do you feel left out?", "How often do you feel isolated from others?", and "How often do you feel alone?". Items were coded "hardly ever" (0), "some of the time" (1), or "often" (2). Items were summed to produce a scale from 0 to 8 (Cronbach α: Dunedin age 38 = 0.85; Dunedin age 45 = 0.84; E-Risk age 18 = 0.83). In the E-Risk Study, childhood social isolation and age-18 loneliness were modestly

correlated (r = 0.15). Childhood social isolation in the Dunedin Study showed similar correlations with loneliness measured at age 38 (r = 0.13) and age 45 (r = 0.11).

2.3. Measures of inflammation

2.3.1. CRP (mg/L)

In the TRIAGE Study, plasma hsCRP was routinely analysed at the Department of Clinical Biochemistry, North Zealand University Hospital, using a Dimension Vista 1500 (Siemens Medical Solutions Diagnostics). In the Dunedin Study, serum hsCRP was measured on a Cobas c702 analyser (Roche Diagnostics GmbH) at age 45, using a particle-enhanced immunoturbidimetric assay. The intraassay and interassay coefficients of variation (CVs) reported by the manufacturer were 0.28–1.34 % and 2.51–5.70 %, respectively. In the E-Risk Study, plasma hsCRP was measured using Quantikine ELISA Kit DCRP00 (R&D Systems, Minneapolis, MN) following the manufacturer's protocol. The CV was 5.6 %.

2.3.2. IL-6 (pg/mL)

In the TRIAGE Study, serum IL-6 was measured on a Cobas 8000 analyzer, using a Roche assay. In the Dunedin Study, serum IL-6 was measured on a Cobas e602 analyzer at age 45, using an electrochemiluminescence immunoassay. The intraassay and interassay CVs reported by the manufacturer were 2.5–6.0 % and 2.9–8.5 %, respectively. In the E-Risk Study, plasma IL-6 was measured using Quantikine HS ELISA Kit HS600C (R&D Systems) following the manufacturer's protocol. The CV was 12.6 %.

2.3.3. suPAR

Plasma suPAR at admission in the TRIAGE Study, at age 45 in the Dunedin Study, and age 18 in the E-Risk Study was analysed with the suPARnostic AUTO Flex ELISA (ViroGates A/S, Birkerød, Denmark) following the manufacturer's protocol, as previously described (Rasmussen et al., 2020, 2021). The detection limit of the assay was 0.1 ng/mL. In the TRIAGE Study, the CV reported by the manufacturer was 2.3–6.0 %. In the Dunedin Study, the intraassay correlation of repeat measurements of the same sample was r = 0.98 and CV = 2.4 %, and the interassay correlation was r = 0.81 and CV = 12.8 %. In the E-Risk Study, the CV was 6 %.

2.4. Covariates

2.4.1. Clinical characteristics

BMI (kg/m^2) and *current daily smoking* were recorded at admission in the TRIAGE Study, at age 45 in the Dunedin Study, and at age 18 in the E-Risk Study. *Use of anti-inflammatory medication* at or near the time of blood draw was assessed in the Dunedin Study and the E-Risk Study, as previously described (Rasmussen et al., 2020; 2021).

2.4.2. Demographics

Sex was included as a covariate in all analyses. In the TRIAGE Study, age was controlled for in addition. In the Dunedin Study, the childhood SES of participants' families was measured using a 6-point scale that assessed parents' occupational statuses, defined based on average income and educational levels derived from the NZ Census. The highest occupational status of either parent was averaged across the childhood assessments (Poulton et al., 2002). In E-Risk, a composite measure of childhood SES was derived based on the family's social class, total household income, and the parents' highest educational qualification (Trzesniewski et al., 2006).

2.4.3. Depression

In the Dunedin Study at age 45 and the E-Risk Study at age 18, depression was assessed based on interviews performed with the *Diagnostic Interview Schedule* (Robins et al., 1995) and diagnoses were made according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (DSM-5) (American Psychiatric Association, 2013).

2.5. Statistical analysis

Continuous variables are reported as median (interquartile range; IQR) or mean (SD), and categorical variables as n (%). While suPAR is normally distributed, CRP and IL-6 were log-transformed to improve normality of their distributions. We used continuous measures of ln (CRP), ln(IL-6), and suPAR for the analyses.

To test associations between living alone, social isolation, or loneliness with inflammatory biomarkers, we used Ordinary Least Squares (OLS) regression. Multivariable regression analyses were adjusted for sex, BMI, and smoking, and additionally for childhood SES, depression, and use of anti-inflammatory medication in Dunedin and E-Risk. We report standardized regression coefficients with 95 % confidence intervals (CIs). In E-Risk, the standard errors were adjusted to control for the nonindependence of observations of twins within families (Williams, 2000).

Where significant associations were detected in the E-Risk cohort, these were further interrogated by capitalizing on the twin design. Fixed effects regression models were conducted, using the family unit as the panel variable, in order to test whether within-sibling pair differences in social isolation or loneliness were associated with within-sibling pair differences in inflammation. This approach enables unmeasured family-level sources of confounding, such as the shared environment and some genetic influences, to be held constant. In the case of monozygotic twins, who are matched for their genomes as well as the shared environment, all genetic influences are controlled for (Pingault et al., 2018).

To test whether the combination of both social isolation and loneliness exerted a multiplicative effect on inflammation, we conducted follow-up regression analyses in the Dunedin and E-Risk samples, in which each inflammatory marker was regressed on social isolation, loneliness, and an interaction term between the two.

Statistical analyses were performed in SAS Enterprise Guide v. 7.15 (SAS Institute Inc, Cary, NC) and Stata 16 (StataCorp, 2019). Analyses reported here were pre-registered (https://sites.duke.edu/moffittcaspiprojects/projects_2019/) and checked for reproducibility by an independent data analyst, who derived the code by working from the manuscript and applied it to a fresh copy of the dataset. A $p < 0.05$ was a priori designated as statistically significant.

3. Results

This study included data from three cohorts: the Danish TRIAGE cohort of acutely admitted medical patients (n = 6,144), the New Zealand population-representative Dunedin birth cohort (n = 881), and the UK population-representative E-Risk twin cohort (n = 1,448). Participants' characteristics and demographics are reported in Table 1. The patients were older with a mean age of 60.4 years at inclusion, while participants in the two population-based cohorts were 45 or 18 years old, respectively, at the most recent data collections. There were slightly more current smokers in the patient population (24.5 %) compared to Dunedin (20.3 %) and E-Risk (23.1 %)—despite smoking status being unknown for a large proportion of TRIAGE patients (21.2 %). Participants from Dunedin or E-Risk included in the current study did not differ significantly from other participants alive at age 45 and age 18, respectively, on childhood SES (Dunedin: t = -1.24, p = 0.22; E-Risk: $\chi 2$ = 1.46, p = 0.48).

3.1. Is living alone associated with inflammation in acutely admitted medical patients?

In the TRIAGE Study, acutely admitted medical patients who were living alone had significantly higher median levels of CRP (5.8 mg/L [IQR 2.9–24.2] vs. 4.8 mg/L [IQR 2.9–22.7], p = 0.043), IL-6 (9.3 pg/

Table 1
Cohort characteristics.

	TRIAGE[a] Mean (SD) or n (%)	DUNEDIN (Age 45)[b] Mean (SD) or n (%)	E-RISK (Age 18)[c] Mean (SD) or n (%)
Total	6,144	881	1448
Male	3016 (49.1)	446 (50.6)	675 (46.6)
Female	3128 (50.9)	435 (49.4)	773 (53.4)
Age (years)	60.4 (19.9)	45	18
BMI	25.5 (5.0)	28.5 (5.8)	22.9 (4.6)
Smoking			
Current smoker	1,504 (24.5)	179 (20.3)	334 (23.1)
Non-smoker	3,340 (54.4)	700 (79.5)	1112 (76.9)
Unknown	1,300 (21.2)	2 (0.2)	–
Anti-inflammatory medication	–	252 (28.6)	17 (1.2)
Childhood SES, mean	–	3.78 (1.14)	–
Low SES	–	–	487 (33.6)
Middle SES	–	–	485 (33.5)
High SES	–	–	476 (32.9)
Loneliness or isolation			
Childhood social isolation	–	−0.03 (0.97)	455 (33.0)
UCLA loneliness scale			
Age 18	–	–	1.53 (1.9)
Age 38	–	1.43 (1.89)	–
Age 45	–	1.18 (1.75)	–
Living alone	1,326 (21.6)	–	–
Depression			
Age 18	–	–	279 (19.3)
Age 38	–	136 (15.6)	–
Age 45	–	137 (15.6)	–
Inflammation			–
CRP (mg/L)	27.35 (51.80)[d]	2.72 (5.62)	2.35 (3.77)
IL-6 (pg/mL)	78.07 (595.92)[d]	2.16 (2.62)	1.23 (1.24)
suPAR (ng/mL)	5.47 (3.62)[d]	3.03 (1.06)	3.23 (0.93)

[a]In the TRIAGE Study, information was missing on BMI for n = 475 patients; on smoking for n = 1,300; on CRP for n = 260; on IL-6 for n = 623; and on suPAR for n = 350.
[b]In the Dunedin Study, information was missing on BMI for n = 3 participants; on smoking for n = 2; on childhood SES for n = 5; on childhood social isolation for n = 7; on UCLA loneliness scale for n = 8 and n = 3 at age 38 and age 45, respectively; on depression for n = 8 and n = 3 at age 38 and age 45, respectively; on CRP for n = 2; on IL-6 for n = 5; and on suPAR for n = 6.
[c]In the E-Risk Study, information was missing on BMI for n = 25 participants; on smoking for n = 2; on childhood social isolation for n = 71; on UCLA loneliness scale for n = 7; on depression for n = 2; on CRP for n = 18; on IL-6 for n = 8; and on suPAR for n = 4.
[d]Median (interquartile range) inflammatory biomarker levels in TRIAGE: CRP: 5.08 mg/L (2.90–22.90); IL-6: 7.67 pg/mL (3.37–23.05); suPAR: 4.40 ng/mL (3.40–6.20).
Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin-6; SD, standard deviation; SES, socioeconomic status; suPAR, soluble urokinase plasminogen activator receptor.

mL [IQR 4.0–29.3] vs. 7.3 pg/mL [IQR 3.2–21.9], $p < 0.0001$), and suPAR (5.2 ng/mL [IQR 3.9–7.2] vs. 4.2 ng/mL [IQR 3.3–5.9], $p < 0.0001$) compared with patients who were not living by themselves (Fig. 1).

However, in regression analyses adjusted for sex and age, patients living alone had higher suPAR levels, but not CRP and IL-6 (Table 2). These results remained unchanged when further controlling for BMI and smoking (Table 2).

3.2. Is childhood social isolation longitudinally associated with inflammation in adulthood?

Next, we turned to the longitudinal Dunedin Study to examine whether there were longitudinal associations between prospectively measured childhood social isolation or adult loneliness measured at an earlier time point (age 38) with inflammation at midlife (age 45) in a population-representative cohort. Participants who had experienced childhood social isolation or age-38 loneliness had higher CRP, IL-6, and suPAR at age 45, after controlling for sex (and age by design) (Table 3). The associations between childhood social isolation or age-38 loneliness with elevated age-45 suPAR held after controlling for childhood SES, and age-45 BMI, smoking, concurrent depression, and anti-inflammatory medication. In contrast to suPAR, childhood social isolation or age-38 loneliness were not significantly associated with age-45 CRP or IL-6 levels when controlling for age-45 BMI and smoking or further for additional covariates (Table 3).

We then investigated the associations of childhood social isolation in the E-Risk cohort of young adults to examine if effects of social isolation on inflammation appear earlier in life. Participants who had experienced childhood social isolation had higher CRP, IL-6, and suPAR at age 18, after controlling for sex (and age by design) (Table 4). This association remained significant for suPAR, but not for CRP or IL-6, after controlling for BMI and smoking. The association for suPAR further survived controls for childhood SES, concurrent depression at age 18, and use of anti-inflammatory medication (Table 4). However, the within-family fixed effect of social isolation on suPAR was negligible and non-significant ($\beta = 0.04$ [95 % CI −0.03; 0.10]). This indicates that socially isolated individuals did not show greater inflammation than their non-isolated siblings, and thus the associations between social isolation and these markers in 18-year-olds are explained by common familial sources of confounding, such as genetic or shared environment influences affecting both twins' inflammation levels.

3.3. Is adult loneliness cross-sectionally associated with inflammation?

In the Dunedin Study, we also examined whether there were any cross-sectional associations between adult loneliness with inflammation at midlife, age 45. After controlling for sex, participants who were lonelier at age 45 had higher suPAR levels at age 45, but not CRP or IL-6 (Table 3). The association with suPAR remained significant after controlling for childhood SES, and age-45 BMI, smoking, and concurrent depression. Further controlling for use of anti-inflammatory medication did not change any of the results.

Meanwhile, in the E-Risk Study, participants who were lonely at age 18 did not exhibit elevated levels of IL-6 or suPAR (Table 4). Interestingly, they had lower levels of CRP at age 18, and this association remained significant after controlling for all covariates. However, within-sibling pair differences in loneliness showed no association with within-pair differences in CRP ($\beta = 0.00$ [95 % CI −0.08; 0.07]), suggesting that the negative association observed between these variables in 18-year-olds was also accounted for by unmeasured familial confounds.

3.4. Do social isolation and loneliness have a multiplicative effect?

No significant social isolation × loneliness interactions were observed for the three inflammation markers, in either the Dunedin or the E-Risk samples.

4. Discussion

The present study tested associations between deficits in social relationships and markers of inflammation. It advances the existing literature on this topic by including replications across multiple cohorts of different ages, study designs, use of multiple markers of inflammation, and genetically-sensitive methods. Across all three cohorts, social isolation was associated with elevated inflammation. This included findings from a clinical cohort of medical patients presenting to a hospital, in addition to two independent population-representative birth cohorts. While the cross-sectional association between social isolation and inflammation observed in the patient cohort could be speculated to be a consequence of sickness leading to more social isolation (reverse

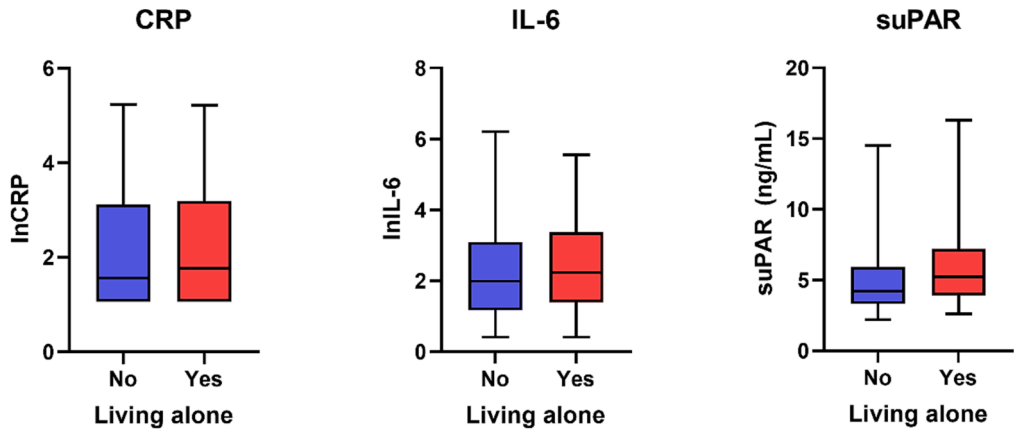

Fig. 1. Blood levels of inflammatory biomarkers (CRP, IL-6, and suPAR) in acutely admitted medical patients from the TRIAGE cohort. Boxes indicate medians with interquartile ranges, and whiskers indicate 95 % confidence intervals. CRP and IL-6 are log-transformed (natural logarithm). CRP, C-reactive protein; IL-6, interleukin-6; suPAR, soluble urokinase plasminogen activator receptor.

Table 2
Associations between living alone and inflammation at admission in the TRIAGE Study.

	Adjusted for sex and age			Adjusted for sex, age, BMI, and smoking		
Variable	**N**	**β (95 % CI)**	**P**	**N**	**β (95 % CI)**	**P**
Living alone						
ln (CRP)[a]	5884	−0.02 (-0.05 to 0.003)	0.08	5424	−0.02 (-0.05 to 0.006)	0.13
ln(IL-6)[a]	5518	−0.02 (-0.04 to 0.007)	0.16	5207	−0.02 (-0.04 to 0.01)	0.18
suPAR	5791	0.05 (0.03 to 0.08)	**<0.0001**	5461	0.06 (0.03 to 0.08)	**<0.0001**

[a] CRP and IL-6 were log-transformed prior to analysis.Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; suPAR, soluble urokinase plasminogen activator receptor.

causation), the longitudinal associations reported in the Dunedin and E-Risk cohorts provide support for the theory that social isolation precedes inflammation. Consistent with prior research (e.g., Danese et al., 2009; Shankar et al., 2011), social isolation rather than loneliness emerged as the stronger candidate in predicting risk of inflammation in mid-life. However, findings in younger adults were mixed, and suggested a role of familial confounding in the associations between social isolation or loneliness and inflammation at this stage of the lifespan.

Previous studies have found associations between social isolation or loneliness with the traditional inflammation markers CRP and IL-6 (Van Bogart et al., 2022; Cudjoe et al., 2022; Hackett et al., 2012; Mezuk et al., 2016; Nersesian et al., 2018; Pavela et al., 2018; Shiovitz-Ezra and Parag, 2019). We found, in all three cohorts, that the novel biomarker suPAR yielded more consistent associations with social isolation than the more commonly used CRP and IL-6. The latter are inflammation markers associated with the acute phase response, whereas suPAR may be an indicator of more systemic chronic inflammation (Marsland, 2021; Rasmussen et al., 2021). This is consistent with the conceptualization of social isolation as a cumulative stressor that becomes biologically embedded over time (Caspi et al., 2006).

With regard to loneliness, previous studies have typically found either no significant association with CRP, or a positive association. The findings in the Dunedin cohort show no significant association with loneliness when lifestyle-related confounders such as BMI and smoking are taken into account. Meanwhile, among the 18-year-old E-Risk participants, a significant association was found, but in the opposite direction to that which might have been expected. Why lonelier 18-year-olds would show below-average CRP levels is unclear. One possibility is that at this age, lonelier individuals are spending less time than their peers in busy social environments where interpersonal transmission of pathogens is more likely. On the other hand, the null findings of the within-twin pair analysis point to familial confounding, with genetic or shared family environment factors affecting both twins' inflammation levels. Taken together, the findings from the E-Risk Study do not support an association between loneliness and CRP in young adulthood. However, it bears consideration that a longer interval of time may be required to detect such an association, given that childhood social isolation showed more consistent associations with an indicator of chronic inflammation in adulthood than with markers of acute inflammation. As such, the findings are somewhat inconclusive, and there would be merit in further investigation in this age group, with longer follow-ups.

The measures used in this study assessed very specific aspects of social relationships. The measures of social isolation, which differed across the three cohorts, covered both structural deficits of social relationships (e.g., living alone, exclusion by peers) and also the quality of those relationships (e.g., the extent to which the children are disliked or do not get along with others). The measure of loneliness, by contrast, primarily concerns subjective perceptions about the functional aspects of social relationships (Valtorta et al., 2016). The pattern of findings suggests that the structural features and quality of social relationships may have greater implications for inflammation compared to more subjective and functional aspects of those relationships (Walker et al., 2019), though this remains to be tested further. In addition, given the multifaceted nature of social connection (Holt-Lunstad, 2018), it is possible that other aspects of social relationships not measured here may also be important predictors of health outcomes. Therefore, while the present study captures specific but important aspects of social relationships that may have implications for inflammation, future research should explore an expanded range of dimensions of social connection to gain a more comprehensive understanding of their roles in health and disease.

Our analyses revealed that social isolation and loneliness were associated with inflammation even after controlling for BMI and smoking, supporting the hypothesis of a direct, biological effect of social isolation/loneliness on inflammation, rather than an effect mediated by health-related behaviors. A prevailing hypothesis for such a direct link involves the hypothalamic–pituitary–adrenal (HPA) axis. Impoverishment of social connection may act as a chronic stressor, contributing to dysregulation of the HPA axis and downstream effects on the inflammatory response (Danese and McEwen, 2012). However, we did not have data with which to explore this mechanism in our cohorts.

Overall, our findings in the current study revealed more significant

Table 3
Longitudinal and cross-sectional associations between childhood social isolation, age 38 loneliness, or age 45 loneliness with age 45 inflammation markers in the Dunedin Study.

	ln(CRP) at age 45			ln(IL-6) at age 45			suPAR at age 45		
Variable and covariates	**N**	**β (95 % CI)**	**P**	**N**	**β (95 % CI)**	**P**	**N**	**β (95 % CI)**	**P**
Childhood social isolation									
Sex	872	0.13 (0.07; 0.20)	**<0.0001**	869	0.11 (0.05; 0.17)	**0.0006**	868	0.18 (0.12; 0.25)	**<0.0001**
Sex, BMI, smoking	868	0.03 (-0.03; 0.08)	0.41	865	0.03 (-0.03; 0.09)	0.34	865	0.12 (0.05; 0.18)	**0.0004**
Sex, BMI, smoking, SES, depression	862	0.02 (-0.04; 0.08)	0.49	859	0.03 (-0.03; 0.09)	0.37	860	0.11 (0.05; 0.18)	**0.0007**
Sex, BMI, smoking, SES, depression, anti-inflammatory medication	862	0.02 (-0.04; 0.08)	0.57	859	0.03 (-0.03; 0.09)	0.39	860	0.11 (0.05; 0.17)	**0.0007**
UCLA loneliness scale at age 38									
Sex	871	0.12 (0.05; 0.19)	**0.0003**	868	0.06 (0.002; 0.13)	**0.044**	867	0.16 (0.09; 0.22)	**<0.0001**
Sex, BMI, smoking	867	0.05 (-0.01; 0.10)	0.12	864	0.002 (-0.06; 0.06)	0.94	864	0.11 (0.05; 0.18)	**0.0003**
Sex, BMI, smoking, SES, depression	860	0.04 (-0.02; 0.10)	0.24	857	0.001 (-0.06; 0.06)	0.97	858	0.10 (0.04; 0.17)	**0.0017**
Sex, BMI, smoking, SES, depression, anti-inflammatory medication	860	0.03 (-0.03; 0.09)	0.34	857	−0.004 (-0.06; 0.06)	0.88	858	0.10 (0.04; 0.16)	**0.0024**
UCLA loneliness scale at age 45									
Sex	876	0.06 (-0.01; 0.12)	0.09	873	0.05 (-0.01; 0.11)	0.11	872	0.16 (0.10; 0.23)	**<0.0001**
Sex, BMI, smoking	873	0.01 (-0.05; 0.07)	0.76	870	0.02 (-0.04; 0.07)	0.59	870	0.13 (0.06; 0.19)	**<0.0001**
Sex, BMI, smoking, SES, depression	868	−0.003 (-0.06; 0.06)	0.93	865	0.01 (-0.05; 0.07)	0.66	866	0.11 (0.05; 0.18)	**0.0006**
Sex, BMI, smoking, SES, depression, anti-inflammatory medication	868	−0.01 (-0.07; 0.05)	0.82	865	0.01 (-0.05; 0.07)	0.70	866	0.11 (0.05; 0.18)	**0.0007**

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; SES, socioeconomic status; suPAR, soluble urokinase plasminogen activator receptor.

Table 4
Longitudinal and cross-sectional associations between childhood social isolation or age 18 loneliness with age 18 inflammation markers in the E-Risk Study.

	ln(CRP) at age 18			ln(IL-6) at age 18			suPAR at age 18		
Variable and covariates	**N**	**β (95 % CI)**	**P**	**N**	**β (95 % CI)**	**P**	**N**	**β (95 % CI)**	**P**
Childhood social isolation									
Sex	1359	0.06 (0.00; 0.12)	**0.04**	1369	0.07 (0.01; 0.12)	**0.01**	1373	0.13 (0.07; 0.18)	**<0.001**
Sex, BMI, smoking	1335	0.02 (-0.03; 0.08)	0.78	1345	0.04 (0.00; 0.09)	0.11	1349	0.06 (0.05; 0.12)	**0.02**
Sex, BMI, smoking, SES, depression	1333	0.03 (-0.03; 0.08)	0.33	1343	0.04 (-0.01; 0.09)	0.13	1347	0.05 (0.00; 0.11)	**0.05**
Sex, BMI, smoking, SES, depression, anti-inflammatory medication	1333	0.03 (-0.03; 0.08)	0.34	1343	0.04 (-0.01; 0.10)	0.12	1347	0.05 (0.00; 0.11)	**0.05**
UCLA loneliness scale at age 18									
Sex	1423	−0.08 (-0.13; −0.02)	**0.004**	1433	−0.04 (-0.09; 0.01)	0.12	1437	−0.01 (-0.06; 0.05)	0.82
Sex, BMI, smoking	1398	−0.07 (-0.13; −0.02)	**0.004**	1408	−0.04 (-0.09; 0.01)	0.11	1412	−0.02 (-0.07; 0.03)	0.51
Sex, BMI, smoking, SES, depression	1396	−0.06 (-0.11; −0.01)	**0.03**	1406	−0.03 (-0.09; 0.02)	0.27	1410	−0.03 (-0.08; 0.03)	0.36
Sex, BMI, smoking, SES, depression, anti-inflammatory medication	1396	−0.06 (-0.11; −0.01)	**0.03**	1406	−0.03 (-0.09; 0.03)	0.30	1410	−0.03 (-0.08; 0.03)	0.36

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; SES, socioeconomic status; suPAR, soluble urokinase plasminogen activator receptor.

associations between social isolation and inflammation compared to loneliness. This could reflect that objective social isolation indeed confers more risk for inflammation compared to the subjective experience of loneliness, although past related research has found that the association between objective social isolation and health outcomes, such as sleep disturbance, depression, and fatigue, depends on the subjective experience of feeling socially isolated (Cho et al., 2019). In addition, it has previously been reported that individuals who are both lonely and socially isolated have the highest health risk (O'Súilleabháin et al., 2019); however, we found no interaction between social isolation and loneliness in our studies.

The results of the within-sibling pair analyses do not support causal associations between deficits in social relationships and inflammation. However, nor do they entirely rule them out. The 18-year-olds in the E-Risk cohort may have been too young for statistically-robust long-term effects of social isolation or loneliness on inflammation to be detectable. The associations detected in the older TRIAGE and Dunedin samples are therefore not necessarily negated; instead, this finding signifies the need for systematic age-group comparisons and for tests of these associations in genetically-sensitive samples of adults in mid- to late-life.

The results have implications for theory, research, and clinical practice. For theory, the results support the theory that social isolation might affect downstream health in adulthood, in part, through systemic chronic inflammation. Systemic chronic inflammation is a major driver

in the development and progression of many major chronic diseases (Furman et al., 2019), and systemic chronic inflammation might be one biological pathway through which social isolation becomes embedded within people's physiology. Social isolation might increase detrimental health behaviours, such as smoking or low levels of physical activity, that may increase or work in concert with systemic inflammation to result in poorer health. The findings further suggest that social isolation rather than subjective measures of loneliness is more important to the development of systemic inflammation, and our longitudinal analyses of childhood social isolation with adult inflammation provide support for the existing theory that the foundation for systemic chronic inflammation is laid already in childhood.

For research, the results suggest that studies on social isolation might benefit from using biomarkers of chronic inflammation, such as suPAR, rather than CRP or IL-6. suPAR can be used as a quantifiable intermediate outcome between childhood or early-life social isolation with more distal outcomes such as disease development or mortality, as suPAR has repeatedly been shown to be strongly associated with poor health, disease development, and mortality (Rasmussen et al., 2021). Thus, intervention studies could use suPAR as an effect measure to assess the effect of various interventions aimed at reducing social isolation, without having to wait many years for disease outcomes to develop.

For clinical practice, the results point to systemic chronic inflammation as a potential intervention target to improve health for people who have been socially isolated. This is also of importance among clinical populations, where social isolation in addition to medical conditions might increase the patients' levels of systemic inflammation. The findings also attest to the importance of timely intervention to reduce social isolation before it can become biologically embedded. However, the evidence base on effective interventions is currently limited (Williams et al., 2021).

4.1. Limitations

The study has some limitations. First, direct measures of social isolation and loneliness were not collected in the clinical TRIAGE Study, and "living alone" was used as a proxy for social isolation, even though individuals who are living alone are not necessarily socially isolated or lonely. Additionally, we did not have information on anti-inflammatory medication use for the patients. Second, the TRIAGE Study was cross-sectional, and the association might have arisen if inflammation-related sickness leads patients to become socially isolated. However, the social isolation-inflammation association was also observed in two prospective studies that assessed isolation in childhood. Third, biomarker data were only available for 1,418 and 881 participants in the E-Risk and Dunedin Studies, respectively; however, no childhood SES differences were found between participants who did and did not have biomarker data available. Fourth, effect sizes were modest. Fifth, we do not have inflammation data available in childhood, preventing us from analysing the association of presence of or improvements in childhood social isolation with inflammation trajectories over time. Furthermore, this means we cannot rule out the possibility that elevated inflammation was present before social isolation or loneliness occurred. Sixth, we were able to identify childhood social isolation, adult loneliness, and living alone as risk factors associated with elevated suPAR levels, but due to the observational study design, we cannot rule out non-causal, alternative explanations of the associations. Testing interventions aimed at reducing the impact of social isolation and loneliness and their effect on suPAR would be informative.

5. Conclusion

Using multiple cohorts of differing ages, the present study interrogated the differential associations of social isolation and loneliness with multiple markers of inflammation. The findings indicate that social isolation was more consistently associated with inflammation than loneliness, emphasising the importance of clearly demarcating these two constructs in research. Furthermore, inflammatory outcomes of childhood social isolation can be observed more clearly in mid-adulthood than in young adulthood. This being the case, suPAR as a measure of chronic rather than acute inflammation may be a particularly reliable indicator of the inflammatory burden of social isolation, and this is supported by the present findings.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JEO is a named inventor on patents on suPAR as a prognostic biomarker. The patents are owned by Copenhagen University Hospital Amager and Hvidovre, Denmark, and is licensed to ViroGates A/S. JEO is a co-founder, shareholder, and CSO of ViroGates A/S. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.11.022.

References

Achenbach, T.M., 1991a. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, VT.

Achenbach, T.M., 1991b. Manual for the Teacher's Report Form and 1991 Profile. Burlington, VT.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. American Psychiatric Association, Arlington, VA.
Balter, L.J.T., Raymond, J.E., Aldred, S., Drayson, M.T., Jet, J.C.S., van Zanten, V., Higgs, S., Bosch, J.A., 2019. Loneliness in Healthy Young Adults Predicts Inflammatory Responsiveness to a Mild Immune Challenge in Vivo. Brain Behav. Immun. 82, 298–301.
Bogart, V., Karina, C.G., Engeland, M.J., Sliwinski, K.D., Harrington, E.L., Knight, R.Z., Scott, S.B., Graham-Engeland, J.E., 2022. The Association Between Loneliness and Inflammation: Findings From an Older Adult Sample. Front. Behav. Neurosci. 15, 801746.
Botha, S., Fourie, C.M.T., Schutte, R., Eugen-Olsen, J., Pretorius, R., Schutte, A.E., 2015. Soluble Urokinase Plasminogen Activator Receptor as a Prognostic Marker of All-Cause and Cardiovascular Mortality in a Black Population. Int. J. Cardiol. 184, 631–666.
Bourassa, K.J., Rasmussen, L.J.H., Danese, A., Eugen-Olsen, J., Harrington, HonaLee, Houts, R., Poulton, R., Ramrakha, S., Sugden, K., Williams, B., Moffitt, T.E., Caspi, A., 2021. Linking Stressful Life Events and Chronic Inflammation Using SuPAR (Soluble Urokinase Plasminogen Activator Receptor). Brain Behav. Immun. 97, 79–88.
Cacioppo, J.T., Hawkley, L.C., Ernst, J.M., Burleson, M., Berntson, G.G., Nouriani, B., Spiegel, D., 2006. Loneliness within a Nomological Net: An Evolutionary Perspective. J. Res. Pers. 40 (6), 1054–1085.
Caspi, A., Harrington, H., Moffitt, T.E., Milne, B.J., Poulton, R., 2006. Socially Isolated Children 20 Years Later: Risk of Cardiovascular Disease. Arch. Pediatr. Adolesc. Med. 160, 805–811.
Cho, J.-J., Olmstead, R., Choi, H., Carrillo, C., Seeman, T.E., Irwin, M.R., 2019. Associations of objective versus subjective social isolation with sleep disturbance, depression, and fatigue in community-dwelling older adults. Aging Ment. Health 23 (9), 1130–1138.
Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social Regulation of Gene Expression in Human Leukocytes. Genome Biol. 8 (9), R189.
Cudjoe, T.K.M., Selvakumar, S., Chung, S.-E., Latkin, C.A., Roth, D.L., Thorpe Jr, R.J., Boyd, C.M., 2022. Getting under the Skin: Social Isolation and Biological Markers in the National Health and Aging Trends Study. J. Am. Geriatr. Soc. 70 (2), 408–414.
Danese, A., McEwen, B.S., 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol. Behav. 106 (1), 29–39.
Danese, A., Moffitt, T.E., Harrington, HonaLee, Milne, B.J., Polanczyk, G., Pariante, C.M., Poulton, R., Caspi, A., 2009. Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease. Arch. Pediatr. Adolesc. Med. 163 (12), 1135–1143.
Elander, J., Rutter, M., 1996. Use and Development of the Rutter Parents' and Teachers' Scales. Int. J. Methods Psychiatr. Res. 6 (2), 63–78.
Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D.W., Fasano, A., Miller, G.W., Miller, A.H., Mantovani, A., Weyand, C.M., Barzilai, N., Goronzy, J.J., Rando, T.A., Effros, R.B., Lucia, A., Kleinstruer, N., Slavich, G.M., 2019. Chronic Inflammation in the Etiology of Disease across the Life Span. Nat. Med. 25 (12), 1822–1832.
Hackett, R.A., Hamer, M., Endrighi, R., Brydon, L., Steptoe, A., 2012. Loneliness and Stress-Related Inflammatory and Neuroendocrine Responses in Older Men and Women. Psychoneuroendocrinology 37 (11), 1801–1809.
Hawkley, L.C., Thisted, R.A., Masi, C.M., Cacioppo, J.T., 2010. Loneliness Predicts Increased Blood Pressure: 5-Year Cross-Lagged Analyses in Middle-Aged and Older Adults. Psychol. Aging 25 (1), 132–142.
Hayek, S.S., Sever, S., Ko, Y.-A., Trachtman, H., Awad, M., Wadhwani, S., Altintas, M.M., Wei, C., Hotton, A.L., French, A.L., Sperling, L.S., Lerakis, S., Quyyumi, A.A., Reiser, J., 2015. Soluble Urokinase Receptor and Chronic Kidney Disease. N. Engl. J. Med. 373 (20), 1916–1925.
Holt-Lunstad, J., 2018. Why Social Relationships Are Important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection. Annu. Rev. Psychol. 69, 437–458.
Holt-Lunstad, J., Smith, T.B., Baker, M., Harris, T., Stephenson, D., 2015. Loneliness and Social Isolation as Risk Factors for Mortality: A Meta-Analytic Review. Perspect. Psychol. Sci. 10 (2), 227–237.
Hunter, C.A., Jones, S.A., 2015. IL-6 as a Keystone Cytokine in Health and Disease. Nat. Immunol. 16 (5), 448–457.
Kobayashi, L.C., Steptoe, A., 2018. Social Isolation, Loneliness, and Health Behaviors at Older Ages: Longitudinal Cohort Study. Ann. Behav. Med. 52 (7), 582–593.
Lacey, R.E., Kumari, M., Bartley, M., 2014. Social Isolation in Childhood and Adult Inflammation: Evidence from the National Child Development Study. Psychoneuroendocrinology 50, 85–94.
Lyngbæk, S., Marott, J.L., Møller, D.V., Christiansen, M., Iversen, K.K., Clemmensen, P. M., Eugen-Olsen, J., Jeppesen, J.L., Hansen, P.R., 2012. Usefulness of Soluble Urokinase Plasminogen Activator Receptor to Predict Repeat Myocardial Infarction and Mortality in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention. Am. J. Cardiol. 110 (12), 1756–1763.
Marsland, A.L., 2021. SuPAR: A Newer Biomarker of Systemic Chronic Inflammation. Brain Behav. Immun. 98, 263–324.
Matthews, T., Danese, A., Wertz, J., Ambler, A., Kelly, M., Diver, A., Caspi, A., Moffitt, T. E., Arseneault, L., 2015. Social Isolation and Mental Health at Primary and Secondary School Entry: A Longitudinal Cohort Study. J. Am. Acad. Child Adolesc. Psychiatry 54 (3), 225–232.
Matthews, T., Danese, A., Wertz, J., Odgers, C.L., Ambler, A., Moffitt, T.E., Arseneault, L., 2016. Social Isolation, Loneliness and Depression in Young Adulthood: A Behavioural Genetic Analysis. Soc. Psychiatry Psychiatr. Epidemiol. 51 (3), 339–348.
Matthews, T., Danese, A., Gregory, A.M., Caspi, A., Moffitt, T.E., Arseneault, L., 2017. Sleeping with One Eye Open: Loneliness and Sleep Quality in Young Adults. Psychol. Med. 47 (12), 2177–2186.
Matthews, T., Danese, A., Caspi, A., Fisher, H.L., Goldman-Mellor, S., Kepa, A., Moffitt, T. E., Odgers, C.L., Arseneault, L., 2019. Lonely Young Adults in Modern Britain: Findings from an Epidemiological Cohort Study. Psychol. Med. 49 (2), 268–277.
Mezuk, B., Choi, M., DeSantis, A.S., Rapp, S.R., Diez, A.V., Roux, and Teresa Seeman., 2016. Loneliness, Depression, and Inflammation: Evidence from the Multi-Ethnic Study of Atherosclerosis. PLoS One 11 (7), e0158056.
Moffitt, Terrie E., E-Risk Study Team, 2002. Teen-Aged Mothers in Contemporary Britain. J. Child Psychol. Psychiatry 43 (6), 727–742.
Nersesian, P.V., Han, H.-R., Yenokyan, G., Blumenthal, R.S., Nolan, M.T., Hladek, M.D., Szanton, S.L., 2018. Loneliness in Middle Age and Biomarkers of Systemic Inflammation: Findings from Midlife in the United States. Soc. Sci. Med. 209, 174–181.
Odgers, C.L., Caspi, A., Bates, C.J., Sampson, R.J., Moffitt, T.E., 2012a. Systematic social observation of children's neighborhoods using Google Street View: a reliable and cost-effective method. J. Child Psychol. Psychiatry 53 (10), 1009–1017.
Odgers, C.L., Caspi, A., Russell, M.A., Sampson, R.J., Arseneault, L., Moffitt, T.E., 2012b. "Supportive parenting mediates widening neighborhood socioeconomic disparities in children's antisocial behavior from ages 5 to 12. Dev. Psychopathol. 24 (3), 705–721.
O'Súilleabháin, Páraic, S., Gallagher, Stephen, Steptoe, Andrew, 2019. Loneliness, Living Alone, and All-Cause Mortality: The Role of Emotional and Social Loneliness in the Elderly During 19 Years of Follow-Up. Psychosom. Med. 81 (6), 521–526.
Pavela, G., Kim, Y.-I., Salvy, S.-J., 2018. Additive Effects of Obesity and Loneliness on C-Reactive Protein. PLoS One 13 (11), e0206092.
Persson, M., Östling, G., Smith, G., Hamrefors, V., Melander, O., Hedblad, B.o., Engström, G., 2014. Soluble Urokinase Plasminogen Activator Receptor: A Risk Factor for Carotid Plaque, Stroke, and Coronary Artery Disease. Stroke 45 (1), 18–23.
Pingault, J.-B., O'Reilly, P.F., Schoeler, T., Ploubidis, G.B., Rijsdijk, F., Dudbridge, F., 2018. Using Genetic Data to Strengthen Causal Inference in Observational Research. Nat. Rev. Genet. 19 (9), 566–580.
Plesner, L.L., Iversen, A.K.S., Langkjær, S., Nielsen, T.L., Østervig, R., Warming, P.E., Salam, I.A., Kristensen, M., Schou, M., Eugen-Olsen, J., Forberg, J.L., Køber, L., Rasmussen, L.S., Sölétormos, G., Pedersen, B.K., Iversen, K., 2015. The Formation and Design of the TRIAGE Study - Baseline Data on 6005 Consecutive Patients Admitted to Hospital from the Emergency Department. Scand. J. Trauma Resusc. Emerg. Med. 23, 106.
Poulton, R., Caspi, A., Milne, B.J., Thomson, W.M., Taylor, A., Sears, M.R., Moffitt, T.E., 2002. Association between children's experience of socioeconomic disadvantage and adult health: A life-course study. Lancet 360 (9346), 1640–1645.
Poulton, R., Moffitt, T.E., Silva, P.A., 2015. The Dunedin Multidisciplinary Health and Development Study: Overview of the First 40 Years, with an Eye to the Future. Soc. Psychiatry Psychiatr. Epidemiol. 50 (5), 679–693.
Rasmussen, L.J.H., Ladelund, S., Haupt, T.H., Ellekilde, G., Poulsen, J.H., Iversen, K., Eugen-Olsen, J., Andersen, O., 2016. Soluble Urokinase Plasminogen Activator Receptor (SuPAR) in Acute Care: A Strong Marker of Disease Presence and Severity, Readmission and Mortality. A Retrospective Cohort Study. Emerg. Med. J. 33 (11), 769–775.
Rasmussen, L.J.H., Moffitt, T.E., Eugen-Olsen, J., Belsky, D.W., Danese, A., Harrington, H., Houts, R.M., Poulton, R., Sugden, K., Williams, B., Caspi, A., 2019. Cumulative Childhood Risk Is Associated with a New Measure of Chronic Inflammation in Adulthood. J. Child Psychol. Psychiatry 60 (2), 199–208.
Rasmussen, L.J.H., Moffitt, T.E., Arseneault, L., Danese, A., Eugen-Olsen, J., Fisher, H.L., Harrington, H., Houts, R., Matthews, T., Sugden, K., Williams, B., Caspi, A., 2020. Association of Adverse Experiences and Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People. JAMA Pediatr. 174 (1), 38–47.
Rasmussen, L.J.H., Caspi, A., Ambler, A., Danese, A., Elliott, M., Eugen-Olsen, J., Hariri, A.R., Harrington, H., Houts, R., Poulton, R., Ramrakha, S., Sugden, K., Williams, B., Moffitt, T.E., 2021a. Association between Elevated SuPAR, a New Biomarker of Inflammation, and Accelerated Aging. J. Gerontol. A Biolog. Sci. Med. Sci. 76 (2), 318–327.
Rasmussen, L.J.H., Petersen, J.E.V., Eugen-Olsen, J., 2021b. Soluble Urokinase Plasminogen Activator Receptor (SuPAR) as a Biomarker of Systemic Chronic Inflammation. Front. Immunol. 12, 780641.
Rhodes, B., Fürnrohr, B.G., Vyse, T.J., 2011. C-Reactive Protein in Rheumatology: Biology and Genetics. Nat. Rev. Rheumatol. 7 (5), 282–329.
Richmond-Rakerd, L.S., D'Souza, S., Andersen, S.H., Hogan, S., Houts, R.M., Poulton, R., Ramrakha, S., Caspi, A., Milne, B.J., Moffitt, T.E., 2020. Clustering of Health, Crime and Social-Welfare Inequality in 4 Million Citizens from Two Nations. Nat. Hum. Behav. 4 (3), 255–264.
Robins, L.N., Cottler, L., Bucholz, K., Compton, W., 1995. Diagnostic Interview Schedule for DSM-IV. Washington University School of Medicine, St. Louis.
Russell, D.W., 1996. UCLA Loneliness Scale (Version 3): Reliability, Validity, and Factor Structure. J. Pers. Assess. 66 (1), 20–40.
Schaefer, Franz, Howard Trachtman, Elke Wühl, Marietta Kirchner, Salim S. Hayek, Ali Anarat, Ali Duzova, Sevgi Mir, Dusan Paripovic, Alev Yilmaz, Francesca Lugani, Klaus Arbeiter, Mieczyslaw Litwin, Jun Oh, Maria Chiara Matteucci, Jutta Gellermann, Simone Wygoda, Augustina Jankauskiene, Günter Klaus, Jiri Dusek, Sara Testa, Aleksandra Zurowska, Alberto Caldas Afonso, Melissa Tracy, Changli

Wei, Sanja Sever, William Smoyer, Jochen Reiser, and the ESCAPE Trial Consortium and the 4C Study Group. 2017. "Association of Serum Soluble Urokinase Receptor Levels with Progression of Kidney Disease in Children." JAMA Pediatrics 171(11): e172914.

Shankar, A., McMunn, A., Banks, J., Steptoe, A., 2011. Loneliness, Social Isolation, and Behavioral and Biological Health Indicators in Older Adults. Health Psychol. 30 (4), 377–385.

Shiovitz-Ezra, S., Parag, O.a., 2019. Does Loneliness 'Get under the Skin'? Associations of Loneliness with Subsequent Change in Inflammatory and Metabolic Markers. Aging Ment. Health 23 (10), 1358–1366.

Theilade, S., Lyngbaek, S., Hansen, T.W., Eugen-Olsen, J., Fenger, M., Rossing, P., Jeppesen, J.L., 2015. Soluble Urokinase Plasminogen Activator Receptor Levels Are Elevated and Associated with Complications in Patients with Type 1 Diabetes. J. Intern. Med. 277 (3), 362–371.

Thompson, K., Agnew-Blais, J.C., Allegrini, A.G., Bryan, B.T., Danese, A., Odgers, C.L., Matthews, T., Arseneault, L., 2023. Do children with attention-deficit/hyperactivity disorder symptoms become socially isolated? Longitudinal within-person associations in a nationally representative cohort. JAACAP Open 1 (1), 12–23.

Trzesniewski, K.H., Brent Donnellan, M., Moffitt, T.E., Robins, R.W., Poulton, R., Caspi, A., 2006. Low Self-Esteem during Adolescence Predicts Poor Health, Criminal Behavior, and Limited Economic Prospects during Adulthood. Dev. Psychol. 42 (2), 381–390.

Umberson, D., Montez, J.K., 2010. Social Relationships and Health: A Flashpoint for Health Policy. J. Health Soc. Behav. 51 (Suppl), S54–S66.

US Department of Health and Human Services. (2023). *Our epidemic of loneliness and isolation: the US Surgeon General's Advisory on the healing effects of social connection and community*. Washington, DC: US Department of Health and Human Services.

Valtorta, N.K., Kanaan, M., Gilbody, S., Hanratty, B., 2016. Loneliness, Social Isolation and Social Relationships: What Are We Measuring? A Novel Framework for Classifying and Comparing Tools. BMJ Open 6 (4), e010799.

Walker, E., Ploubidis, G., Fancourt, D., 2019. Social Engagement and Loneliness Are Differentially Associated with Neuro-Immune Markers in Older Age: Time-Varying Associations from the English Longitudinal Study of Ageing. Brain Behav. Immun. 82, 224–229.

Williams, R.L., 2000. A Note on Robust Variance Estimation for Cluster-Correlated Data. Biometrics 56 (2), 645–666.

Williams, C.Y.K., Townson, A.T., Kapur, M., Ferreira, A.F., Nunn, R., Galante, J., Phillips, V., Gentry, S., Usher-Smith, J.A., 2021. Interventions to Reduce Social Isolation and Loneliness during COVID-19 Physical Distancing Measures: A Rapid Systematic Review. PLoS One 16 (2), e0247139.