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1 **Loneliness in Healthy Young Adults Predicts Inflammatory Responsiveness to**
2 **a Mild Immune Challenge in Vivo**

3

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16 **Keywords:** loneliness; mild inflammation; immune dysregulation; typhoid vaccination

17 **ABSTRACT**

18 The established link between loneliness and poor health outcomes may stem from
19 aberrant inflammatory regulation. The present study tested whether loneliness predicted the
20 inflammatory response to a standardised in vivo immune challenge. Using a within-subjects
21 double blind placebo-controlled design, 40 healthy men (mean age = 25, SD = 5) received a
22 Salmonella Typhi vaccination (0.025 mg; Typhim Vi, Sanofi Pasteur, UK) and placebo
23 (saline) on two separate occasions. Loneliness was assessed using the R-UCLA loneliness
24 scale. Regression analyses showed that those that reported feeling more lonely exhibited an
25 elevated interleukin-6 response ($\beta = .564$, 95% confidence interval [.003, .042], $p < .05$).
26 This association withstood adjustment for potentially confounding variables, including age,
27 sleep quality, socio-emotional factors, and health factors. The present findings are in line
28 with evidence that loneliness may shift immune system responsivity, suggesting a potential
29 biobehavioural pathway linking loneliness to impaired health.

30

31 **INTRODUCTION**

32 Feeling lonely is surprisingly prevalent in today’s society, with estimates stating that
33 over 15% of British and nearly 40% of US adults report feeling lonely (Office for National
34 Statistics, 2018; Wilson & Moulton, 2010), Loneliness is increasingly recognised as a
35 significant social problem, whereby the British government recently appointed a Minister of
36 Loneliness. One of the several disruptive effects of loneliness is on physical health. For
37 example, meta-analyses show a 30% increased risk of stroke, myocardial infarction, and
38 mortality in lonelier individuals (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015;
39 Steptoe, Shankar, Demakakos, & Wardle, 2013; Valtorta, Kanaan, Gilbody, Ronzi, &
40 Hanratty, 2016).

41 Immune dysregulation, in the form of enhanced inflammatory responsivity, has been
42 proposed as a mechanism underlying the link between loneliness and health risk (Hawkey,
43 Bosch, England, Marucha, & Cacioppo, 2007). This idea has been supported, amongst
44 others, by evidence that inflammatory gene transcription and epigenetics are altered in
45 lonely individuals, together with studies showing increased immune reactivity to
46 psychological stress in lonelier individuals (Brown, Gallagher, & Creaven, 2018; Cole et al.,
47 2007; Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012; Jaremka et al., 2013). Likewise,
48 the inflammatory response to an immune challenge (bacterial endotoxin) is elevated in
49 individuals who report feeling socially disconnected (Moieni, Irwin, Jevtic, Breen, &
50 Eisenberger, 2015), which is predictive of loneliness (Cacioppo et al., 2006). However,
51 whether loneliness itself is associated with inflammatory responsivity has yet to be
52 determined. This proposed hypothesis was tested using an existing data-set. The current
53 study addressed the relationship between individual variation in subjective loneliness and
54 immune reactivity in response to a mild immune-mediated inflammatory stimulus. Analyses
55 were adjusted for potential confounders such as age, sleep quality, socio-emotional factors
56 (i.e., depression, anxiety, social skills, negative mood), and health factors (i.e., body weight,
57 alcohol intake).

58

59 **METHOD**

60 *Participants*

61 The study involved a within-subjects double blind placebo-controlled design,
62 presented in detail elsewhere (Balter et al., 2018). Forty healthy young male students from
63 the University of Birmingham were enrolled (M age = 24.7, SD = 5.2 years). Individuals were
64 excluded if they self-reported a history of or suspected vaccine- or food-related allergy,
65 inflammatory, cardiovascular, neurological, mental health, visual, or immune-related
66 disorder, being a current smoker, and those on any medication 7 days prior to the test days.
67 Participants received research credits or were paid £40. The study was conducted according
68 to the guidelines laid down in the Declaration of Helsinki and all procedures were approved
69 by the local Research Ethics Committee of the National Health Service.

70

71 *Procedures*

72 Participants visited the behavioural immunology laboratory on three separate
73 occasions (one practice session and two test days): questionnaires were completed once
74 during the first visit, except for negative mood, which was rated on each test day (see
75 Materials). This was followed by two test days scheduled at least one week apart. On each
76 test day, participants arrived at the laboratory between 8:00 and 9:00 am. A certified nurse
77 administered Salmonella typhi capsular polysaccharide vaccine (25 μ g in 0.5 mL, Typhim Vi,
78 Sanofi Pasteur, UK) or saline placebo (0.5 mL) via intra-muscular injection in the deltoid
79 muscle of the non-dominant arm; the injection order was counterbalanced across
80 participants. Blood samples were taken before injection, and at 5h30min and 8h post-
81 injection. The time points for the collection of the blood samples was based on the time
82 course and magnitude of a variety of inflammatory markers published previously by our
83 group (see Paine, Ring, Bosch, Drayson, & Veldhuijzen van Zanten, 2013).

84 The current analysis is based on the same sample as in Balter et al., (2018) and
85 stem from secondary analysis of a larger study.

86

87 **MATERIALS**

88 *Questionnaires*

89 Questionnaires were completed in the order as presented below. Higher scores reflect
90 worse functioning.

91 *Alcohol intake.* Average alcohol units per week (0 = 0 units, 1 = 1-5 units, 2 = 7-15
92 units, 3 = >15 units). One unit equals 10ml or 8g of pure alcohol and is equivalent to 1/2 pint
93 of average-strength beer. A standard glass of wine is 2 units of alcohol. The definition of a
94 unit of alcohol was explained to the participant.

95 *Sleep quality.* The total score of the 19-item Pittsburgh Sleep Quality Index was used
96 to assess quality of sleep over a 1-month interval. Internal consistency (Cronbach's alpha; α)
97 is 0.80 for the total score (Carpenter & Andrykowski, 1998).

98 *Anxiety.* The 21-item Beck Anxiety Inventory was used to assess anxiety. The
99 Cronbach's α for non-psychiatric individuals is 0.81 (Beck, Epstein, Brown, & Steer, 1988).

100 *Depression.* The 21-item Beck Depression Inventory (BDI)-II was used to assess
101 depressive feelings (Beck, Steer, & Brown, 1996). The BDI-II boasts high internal
102 consistency among college students (Cronbach's α = 0.93; Dozois, Dobson, & Ahnberg,
103 1998).

104 *Loneliness.* Loneliness was measured via the 20-item revised UCLA Loneliness Scale
105 (R-UCLA). The Cronbach's α reliability coefficient for the R-UCLA is 0.96 (Russell, Peplau, &
106 Cutrona, 1980).

107 *Social skills.* The social skills subscale of the Autism Quotient was used to measure
108 the degree of social skills a person possesses (Baron-Cohen, Wheelwright, Skinner, Martin,
109 & Clubley, 2001). The Cronbach's α for the social skills subscale is 0.75 (Stevenson & Hart,
110 2017).

111 *Mood.* Negative mood on the day of testing was computed by summing five negative
112 subscale scores (anger, confusion, depression, fatigue, and tension) and subtracting the

113 vigour subscale score of the Profile of Mood States Short Form. The Cronbach's α for total
114 negative mood in a healthy sample is 0.88 (Curran, Andrykowski, & Studts, 1995).

115

116 *Anthropomorphic measures*

117 A stadiometer was used to measure height and a body composition measurement
118 was taken using a TANITA BC-545N body composition analyser (Tanita Europe,
119 Amsterdam, The Netherlands).

120

121 *Interleukin-6 analysis*

122 Blood (6 ml) was collected from an antecubital vein in the forearm into a vacutainer
123 containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant (Becton Dickinson
124 Diagnostics, Oxford, United Kingdom). Samples were immediately centrifuged at 1500g for
125 10 min at 4 °C and plasma was aliquoted and stored at -80 °C for later cytokine assessment
126 of plasma interleukin-6 (IL-6) using high-sensitivity ELISA (Quantikine HS Human IL-6
127 ELISA, R&D Systems, UK) in accordance with the manufacturer's instructions. The limit of
128 detection of this assay was 0.11 pg/mL, with an intra-assay coefficient of variation (CV) of
129 4.2%. All samples were well above the detection limit (the sample values ranged between
130 0.33 and 9.62 pg/mL). To minimize assay variation, all samples from the same participants
131 were assayed in the same run.-

132

133 **STATISTICAL ANALYSIS**

134 Data were analysed using SPSS v.24.0 (IBM-SPSS Inc., Chicago, IL, USA). IL-6
135 data of three participants were ~~excluded~~ removed because IL-6 data of three participants
136 were removed because for two participants the inflammation induction did not induce an
137 inflammatory response of two of these three participants showed a high baseline balue (>
138 2.5 SD above mean) that was indicative of a possible immune activation. of high baseline
139 values indicative of a possible infection-Additionally, and 5% of IL-6 data was missing due to
140 occasional failure to take a blood draw. Data were analysed using bivariate correlation

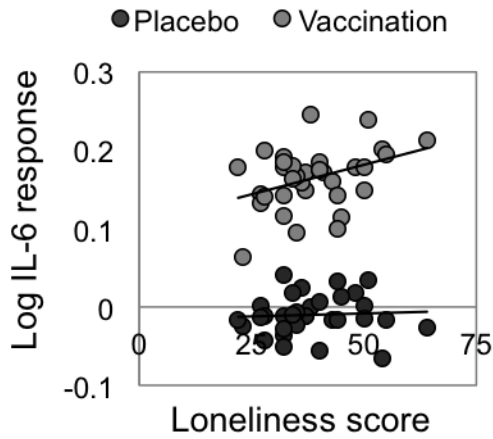
141 analysis and linear regression analysis with log transformed IL-6 response (difference from
142 baseline to peak IL-6 at [either](#) 5h30 or 8h post-injection) in the vaccine condition. Model 1
143 included loneliness, model 2 and 3 additionally included variables previously shown to be
144 associated with inflammation or loneliness: depression, anxiety, negative mood, sleep
145 quality, social skills, alcohol intake (model 2), age, and body mass index (BMI) (model 3).

146

147 **RESULTS**

148 Loneliness scores ranged between 22-64 ($M = 39$, $SD = 10$) and typhoid vaccination
149 increases in IL-6 ranged from 1.1-8.8 pg/mL ($M = 3.8$, $SD = 1.6$) (see also Balter et al.,
150 2018). At baseline, IL-6 was not significantly correlated with loneliness scores ($r(36) = -.123$,
151 $p = .487$). However, as shown in Figure 1, loneliness positively correlated with the IL-6
152 response (difference from baseline to peak IL-6 at [either](#) 5h30 or 8h post-injection) to
153 typhoid vaccination ($r(34) = .383$, $p = .026$). [In 92% of the cases the peak IL-6 occurred at](#)
154 [5h30](#). Analyses using IL-6 responses at a single time point (5h30 or 8h) yielded essentially
155 similar results. None of the other socio-emotional variables significantly correlated with the
156 IL-6 response (Table 1). No significant correlations emerged in the placebo condition (p 's >
157 .60). Regression analysis showed that individual variation in loneliness was associated with
158 the IL-6 response (model 1), independent of depression, anxiety, negative mood, quality of
159 sleep, social skills, alcohol intake (model 2), age and BMI (model 3) (Table 2).

160



162

163 *Figure 1. Correlations between log IL-6 response (difference from baseline to peak IL-6 at*
 164 *[either](#) 5h30 or 8h post-injection) and loneliness separately for the placebo and vaccination*
 165 *condition.*

166

| | IL-6 response |
|---------------|---------------|
| Loneliness | .383* |
| Depression | .053 |
| Anxiety | .060 |
| Negative mood | .106 |
| Social skills | .146 |

174

175 *Table 1. Correlation coefficients between the log IL-6 response (difference from baseline to*
 176 *peak IL-6 at [either](#) 5h30 or 8h post-injection) to vaccination and socio-emotional variables; **
 177 *indicates statistical significance ($p < .05$).*

178

| | <i>t</i> | β | <i>p</i> | 95% CI |
|---------------------------------------|----------|---------|----------|------------|
| | | | | 179 |
| Model 1 (R² = .146) | | | .026* | 181 |
| Loneliness | 2.343* | .383* | .026* | .001 .029 |
| Model 2 (R² = .281) | | | .302 | 183 |
| Loneliness | 2.179* | .517* | .040* | .001 .040 |
| Depression | -0.207 | -.055 | .838 | -.032 .026 |
| Anxiety | 0.404 | .086 | .690 | -.014 .021 |
| Sleep quality | -1.558 | -.321 | .133 | -.029 .004 |
| Negative mood | 0.421 | .105 | .678 | -.019 .028 |
| Social skills | -0.783 | -.182 | .442 | -.025 .011 |
| Alcohol intake | -1.168 | -.238 | .255 | -.026 .007 |
| Model 3 (R² = .347) | | | .325 | 191 |
| Loneliness | 2.407* | .579* | .025* | .003 .042 |
| Depression | -0.772 | -.224 | .449 | -.044 .020 |
| Anxiety | 0.278 | -.069 | .784 | -.024 .018 |
| Sleep Quality | -0.802 | -.182 | .431 | -.026 .011 |
| Negative mood | 0.755 | .194 | .458 | -.016 .033 |
| Social skills | -0.199 | -.056 | .844 | -.025 .020 |
| Alcohol intake | -1.521 | -.374 | .143 | -.034 .005 |
| Age | -1.031 | -.325 | .322 | -.037 .013 |
| BMI | -0.573 | -.121 | .572 | -.021 .012 |
| | | | | 201 |

202

203 *Table 2. Standardised regression coefficients (β), *t*- and *p*-values, and 95% confidence*
 204 *intervals (95% CI) of models predicting the IL-6 response (difference from baseline to peak*
 205 *IL-6 at [either](#) 5h30 or 8h post-injection) to the immune challenge; * denotes statistical*
 206 *significance ($p < .05$).*

207

208

209

210 **DISCUSSION**

211 The results presented here showed that those that reported feeling more lonely
212 exhibited an enhanced inflammatory response to a mild immune stimulus. This association
213 was robust to adjustment of age, BMI, and socio-emotional variables. A prior study showed
214 that feelings of social disconnection were associated with an elevated immune response to
215 endotoxin, an inflammatory stimulus that raises IL-6 about 100-fold (Moieni, Irwin, Jevtic,
216 Breen, Cho, et al., 2015; Moieni, Irwin, Jevtic, Olmstead, et al., 2015). The current study
217 extends this finding to loneliness, showing that a mild inflammatory stimulus, raising IL-6
218 levels about 4-fold, similarly evokes an enhanced inflammatory response in more lonely
219 individuals. Although loneliness and social disconnection tend to co-occur, there is a
220 conceptual distinction between the two, whereby feeling lonely is considered a result of
221 social disconnection (Cacioppo et al., 2006). However, strong genetic overlap between
222 social isolation and loneliness as well as depression has been reported (Matthews et al.,
223 2016). The observation that neither depression, anxiety, social skills nor negative mood
224 were correlated with the inflammatory response, suggest that the relationship between
225 loneliness (or social disconnection, as shown by Moieni et al., (2015)) and immune
226 responsiveness is unlikely to be confounded by other negative socio-emotional factors.

227 Since we and others identified loneliness as a predictor of immune dysregulation,
228 screening for loneliness in populations with inflammation-related complaints, and other high-
229 risk populations such as older adults, may be warranted as a target for further study.
230 Admittedly, a causal role of loneliness remains speculative at this point, but the present
231 findings as well as those of others, do provide a rationale to explore if interventions that
232 focus on reducing feelings of loneliness may simultaneously help ameliorate inflammatory
233 dysregulation. Likewise, evidence of a possible causal role of loneliness might be
234 strengthened by studies that manipulate subjective loneliness for example via a false
235 feedback paradigm (see Lamster, Nittel, Rief, Mehl, & Lincoln, 2017). The current findings

236 are limited in terms of generalizability due to the experimental nature of the study and that
237 only healthy young males were assessed. Despite this consideration, research could assess
238 whether lonely individuals may also have stronger responses to more naturalistic
239 inflammatory insults such as a cold or flu. Furthermore, although the present study was
240 aligned with prior research and was hypothesis driven, the current results stem from
241 secondary analysis of existing data, and replication seems therefore warranted.

242 In summary, the current results showed that, among healthy young adults, those
243 feeling more lonely exhibited a higher inflammatory response to a mild immune challenge,
244 that appeared independent of negative mood and common confounders related to social or
245 health behaviours.

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331

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