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Intelligence and neuroticism in relation to depression and psychological distress: Evidence from two large population cohorts

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ABSTRACT

Background: Neuroticism is a risk factor for selected mental and physical illnesses and is inversely associated with intelligence. Intelligence appears to interact with neuroticism and mitigate its detrimental effects on physical health and mortality. However, the inter-relationships of neuroticism and intelligence for major depressive disorder (MDD) and psychological distress has not been well examined.

Methods: Associations and interactions between neuroticism and general intelligence (*g*) on MDD, self-reported depression, and psychological distress were examined in two population-based cohorts: Generation Scotland: Scottish Family Health Study (GS:SFHS, n = 19,200) and UK Biobank (n = 90,529). The Eysenck Personality Scale Short Form-Revised measured neuroticism and *g* was extracted from multiple cognitive ability tests in each cohort. Family structure was adjusted for in GS:SFHS.

Results: Neuroticism was strongly associated with increased risk for depression and higher psychological distress in both samples. Although intelligence conferred no consistent independent effects on depression, it did increase the risk for depression across samples once neuroticism was adjusted for. Results suggest that higher intelligence may ameliorate the association between neuroticism and self-reported depression although no significant interaction was found for clinical MDD. Intelligence was inversely associated with psychological distress across cohorts. A small interaction was found across samples such that lower psychological distress associates with higher intelligence and lower neuroticism, although effect sizes were small.

Conclusions: From two large cohort studies, our findings suggest intelligence acts a protective factor in mitigating the effects of neuroticism on psychological distress. Intelligence does not confer protection against diagnosis of depression in those high in neuroticism.

Q2 1. Introduction

Major depressive disorder (MDD) is a leading cause of disease burden worldwide [1]. Although MDD aetiology remains elusive, a large proportion of its genetic covariance is attributable to neuroticism [2,3], suggesting a causal relationship. Neuroticism is a partially-heritable personality trait representing high emotionality and stress sensitivity [4], which correlates highly with MDD [5]. Cross-sectional studies suggest a strong positive association between neuroticism and MDD [6–8], whilst higher neuroticism prospectively associates with depression longitudinally [2,9–12], even when controlling for overlapping criteria [13–15] and

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demographics [16,17]. Whist the public health impacts of neuroticism are wide-ranging (for a comprehensive review see Lahey), neuroticism may be an indirect measure of later MDD risk, rather than the causative risk factor itself. Whilst MDD is often recurrent [18], neuroticism is a stable trait [19] suggesting that their correlation is unlikely to be substantially attributable to an effect of MDD on neuroticism.

General intelligence (*g*) is a latent construct theorized to explain the common observation that people who excel in one type of cognitive task tend to excel in others [20]. When reduced to a single factor (*g*) these correlations explain approximately 50% of the covariance between tests. Lower intelligence in early life has been found to be a risk factor for poor physical health [21] and early mortality in adulthood [22,23]. Although research specifically regarding MDD is relatively sparse [24], there is evidence to suggest that *g* is impaired in depression [25,26] with longitudinal studies suggesting lower *g* in childhood or adolescence confers vulnerability to psychopathology in adulthood [27–30].

Psychological distress represents a cluster of emotional symptoms linked to depression [31–33]. Although symptoms of distress are common in population samples [34,35], they indicate only subthreshold mental health problems. With self-report measures of distress [36,37] freely available in epidemiological research, their measurement provides greater detective power to make distinctions between syndrome and subthreshold symptoms. Longitudinal research suggests neuroticism has a strong, direct effect on psychological distress [38]. Low childhood intelligence strongly associates with increased psychological distress in adulthood [27,39], which may precede MDD onset [40]. However, this is not a universal observation, particularly in studies accounting for socioeconomic status (SES).

Intelligence and neuroticism may interact to influence indices of health. A longitudinal study of war veterans [41] found high neuroticism and low cognitive ability were separate risk factors for mortality. Specifically, a 1-standard deviation increase in neuroticism resulted in a 33% increase in mortality; a 1-standard deviation decrease in intelligence associated with a 27% increase in mortality. An interaction (hazards ratio of 0.89) suggested that high neuroticism with low cognitive ability associates with high risk of poor health and reduced lifespan. Furthermore, high cognitive ability moderates the adverse effects of neuroticism on adjustment [42]. Whether similar interactions exist with regard to their effects on depression remains unknown. No investigation has yet examined how intelligence and neuroticism influence risk for MDD and how they may moderate each other's associations in depression and psychological distress. Such an analysis may serve to clarify the mechanisms underlying MDD.

In this study, two large population-based cohorts were examined – Generation Scotland: Scottish Family Health Study (GS: SFHS) [43,44] and UK Biobank [45,46]. As previous studies suggest strong associations of neuroticism with risk of MDD [2,5], the same effect was hypothesised here. We hypothesised that higher intelligence may reduce MDD risk by mitigating the adverse effects of neuroticism, similarly to the interaction identified for mortality [41]. This reasoning transfers to psychological distress, hypothesising a positive association between neuroticism and psychological distress would be ameliorated by higher intelligence.

2. Method

2.1. GS:SFHS Overview

GS:SFHS is a family and population-based cohort recruited throughout Scotland between 2006 and 2011 [43]. During clinic assessment, participants aged 18–98 (n = 24,084) provided clinical, cognitive and biological data. Full details are provided elsewhere [43,44]. The GS:SFHS sample is predominately female (59%), and generally healthier and wealthier than the Scottish population [43]. This study includes 19,200 individuals with complete data of interest. Demographic information from this cohort is provided in Table 1 and within the Supplementary materials.

Study assessments: during clinic assessment, participants were screened for lifetime history of MDD using a structured clinical interview [47]. Diagnosis of MDD follows DSM-IV criteria; if either symptoms of depressive mood or anhedonia are endorsed, a minimum of four further symptoms must also be endorsed. Clinical significance must be endorsed, too (ie., symptoms lasting nearly all day, every day for a minimum of two weeks). This study includes 2481 individuals meeting criteria for lifetime history of MDD (13%), and 16,719 non-MDD cases (87%).

Four cognitive tests measuring intelligence were administered during clinic assessment [43,44]. The Wechsler Digit Symbol Substitution Task [48] measured processing speed. One paragraph from The Weschler Logical Memory Test I & II [49] measured verbal declarative memory. The Verbal Fluency Test measured executive function [48] using phonemic lists of C, F and L. Vocabulary was measured with The Mill-Hill Vocabulary Test [50], using combined junior and senior synonyms. General intelligence (*g*) was extracted from these tests, as the first un-rotated principal component [51], explaining 41% of the variance. Loadings for processing speed,

Table 1
Demographic, clinical, and cognitive characteristics of GS:SFHS and UK Biobank individuals in the current study.

	GS:SFHS			UK Biobank		
	Total (n = 19,200)	Control (n = 16,719)	Lifetime MDD (n = 2481)	Total (n = 90,529)	Control (n = 60,402)	Lifetime MDD (n = 30,127)
Age	47.16 (14.97)	47.23 (15.27)	46.39 (12.89)*	56.64 (8.13)	57.15 (8.16)	55.60 (7.98)*
Sex (% female)	59	57	72*	52	46	65*
Neuroticism	3.84 (3.16)	3.45 (2.94)	6.45 (3.32)*	3.46 (2.86)	2.65 (2.43)	5.09 (2.96)*
GHQ score	15.93 (8.81)	14.93 (7.56)	22.70 (12.77)*	–	–	–
PHQ score	–	–	–	1.36 (1.91)	0.89 (1.33)	2.30 (2.47)*
Wechsler Digit Symbol Substitution Task	72.31 (17.09)	72.45 (17.23)	71.44 (16.06)*	–	–	–
Mill-Hill Vocabulary Test	30.06 (4.76)	30.05 (4.75)	30.15 (4.84)	–	–	–
Weschler Logical Memory Test I & II	31.01 (8.04)	30.99 (8.09)	31.02 (7.68)*	–	–	–
Verbal Fluency Test	25.68 (8.10)	25.60 (8.11)	26.21 (8.05)*	–	–	–
Reaction time	–	–	–	564.00 (119.87)	564.70 (119.98)	562.58 (119.66)*
Visual memory	–	–	–	4.04 (3.21)	4.04 (3.23)	4.04 (3.17)
Verbal-numerical reasoning	–	–	–	6.09 (2.14)	6.07 (2.16)	6.12 (2.11)*
SIMD	3903.82 (1851.91)	3957.58 (1832.28)	3541.51 (1941.03)*	–	–	–
Townsend Score	–	–	–	−1.37 (2.84)	−1.47 (2.77)	−1.06 (2.94)*

GS:SFHS: Generation Scotland: the Scottish Family Health Study; MDD: Major Depressive Disorder; GHQ: General Health Questionnaire; PHQ: Patient Health Questionnaire; SIMD: the Scottish Index of Multiple Deprivation. With the exception of sex, values represent Mean (SD).
* Significantly different from controls at $P < 0.05$.

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vocabulary, verbal declarative memory and executive function were 0.57, 0.68, 0.63 and 0.69 respectively.

The self-reported Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF) [52] measured neuroticism. Twenty-four questions assessed neuroticism and extraversion, with total scores on each subscale ranging from 0–12. Higher scores indicate higher levels of each trait. This scale has been concurrently validated [53] with high reliability [54].

Psychological distress was self-reported using the General Health Questionnaire (GHQ-28) [36]. Twenty-eight items were scored from 0 (“*not at all*”) to 3 (“*much more than usual*”) with a total score ranging from 0–84. Higher scores indicate increased psychological distress.

The Scottish Index of Multiple Deprivation (SIMD) [55] is an official tool which identifies deprivation by combining different indicators (eg., income, crime) into a single index. The SIMD divides Scotland into 6505 small areas based on participant postcode, and assigns them a relative ranking from 1 (most deprived) to 6505 (least deprived).

2.2. UK Biobank Overview

UK Biobank is a population cohort recruited across the UK from 2006–2010. During an extensive baseline assessments [56] participants aged 40–69 (n = 502,682) provided biological, physical, and touch-screen questionnaire measures of socio-demographics (e.g., age, sex), psychosocial factors (e.g., mental health), and cognitive function. UK Biobank represents a wide range of exposures typical within the UK population [57], and has been described in detail elsewhere [45,46]. In this study, 147 individuals were removed from analysis due to participation in GS:SFHS. In total, 90,529 individuals with complete data of interest were included. Demographic information is provided in Table 1 and in the Supplementary materials.

Study assessments: between 2008–2010, a touch-screen questionnaire was added to the protocol to assess probable depression (n = 172,751) [58]. Although depression was not assessed using a precise diagnostic tool, the classification followed a self-report approach within the guidelines of the ICD- 10 [59] and the DSM-IV [60]. Lifetime history of depression was assessed using items relating to the lifetime experience of depressive symptoms and help-seeking for mental health. A detailed description of how this phenotype was derived is provided elsewhere [56]. This study included 30,127 (33%) individuals self-reporting lifetime history of depression, and 60,402 (67%) non-depressed cases.

Three novel cognitive tests were administered via touch-screen questionnaire measuring reaction time, verbal-numerical reasoning, and visual memory [56]. A timed symbol matching test measured reaction time as the mean response time in ms over 12 trials; higher reaction times equate to poorer performance. Thirteen logic/reasoning-type questions assessed verbal-numerical reasoning - the total number of correct answers given within two-minutes was analysed. A visuo-spatial memory task measured the number of errors made when matching card pairs, higher scores reflect poorer cognitive function. From these tests, g was extracted as the first un-rotated principal component [51], explaining 44% of the variance in scores. Loadings onto g were: −0.61 (verbal-numeric reasoning), 0.57 (visual memory), and 0.55 (reaction time).

Neuroticism was assessed using 12 questions from the Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF) [52], administered via a touch-screen questionnaire. A total score from 0–12 was produced, with higher scores reflecting increasing neuroticism.

The first four questions of the Patient Health Questionnaire–9 (PHQ9) [37] were administered by touch-screen questionnaire to measure psychological distress. Responses on a scale from 0 (“*Not at all*”) to 3 (“*Nearly every day*”) were aggregated and a higher total score denoted higher levels of psychological distress.

The Townsend Deprivation Index [61] is a census-based measure of deprivation, incorporating unemployment, non-car ownership, non-home ownership and household overcrowding into a single index. Small geographical areas based on postcode information are allocated Townsend Scores. Higher scores represent greater deprivation.

2.3. Statistical analysis

In GS:SFHS, the MCMCglmm package was used. The Markov Chain Monte Carlo estimator produces generalised linear mixed models for binary outcomes (using the “threshold” family with a probit link function). The threshold link is unique to MCMCglmm, and although produces very similar results to a logit function, threshold links most closely match the underlying assumptions of latent normal errors in pedigree-based mixed effect models [62]. MCMCglmm was essential to control for genetic relatedness of the sample, which was fitted as a random effect using an inverse pedigree matrix. Due to limitations within MCMCglmm with missing predictor variables, only complete data can be used. An interaction was fitted to estimate the moderating effect of g on the contribution of neuroticism to MDD. Another model examined this interaction while conditioning on deprivation. Regression coefficients are reported as Odds-Ratios. In a second set of analyses, GHQ was modelled as a normally distributed outcome variable. Neuroticism and GHQ were standardised to have a mean of zero and a standard deviation of 1. Age (standardised) and sex were used as fixed effects throughout.

In UK Biobank, generalized linear regression analyses were conducted as kinship need not be accounted for. The main effects of neuroticism and g were examined as predictors for self-reported depression. The interaction between neuroticism and g on depression was modelled. Another model examined this interaction while adjusting for deprivation. Generalized linear regressions were fitted with a logit link function and Odds-Ratios reported. A second set of analyses examined psychological distress (PHQ) using linear regression models. Neuroticism and PHQ were standardised to have a mean of zero and a standard deviation of one. Reaction time was log transformed due to a significantly positive skew. Visual memory was transformed with a log + 1 transformation because it was significantly skewed and zero-inflated. All regression analyses co-varied for age, and sex.

3. Results

3.1. GS:SFHS

As seen in Table 1, MDD cases were younger, predominately female, and had higher GHQ and neuroticism scores. No group differences were found in general intelligence; ($t(3243.38) = -1.39$, $P = 0.17$, Cohen’s $d = 0.03$). Group differences were found in processing speed and executive function. MDD cases were from less deprived areas; ($t(3171.20) = 9.93$, $P = 2.20 \times 10^{-16}$, Cohen’s $d = 0.22$). Full statistical output can be found in the Supplementary materials.

3.1.1. Associations of neuroticism and g with MDD status

Higher neuroticism was strongly associated with increased risk for MDD. A 1SD-increase in neuroticism increased MDD risk by an odds-ratio of 3.61 (95% CIs = [3.28, 4.01], $P < 1.00 \times 10^{-4}$). Although no age effects were found, being female increased risk for MDD by an Odds-Ratio of 1.76 (95% CIs = [1.52, 2.03],

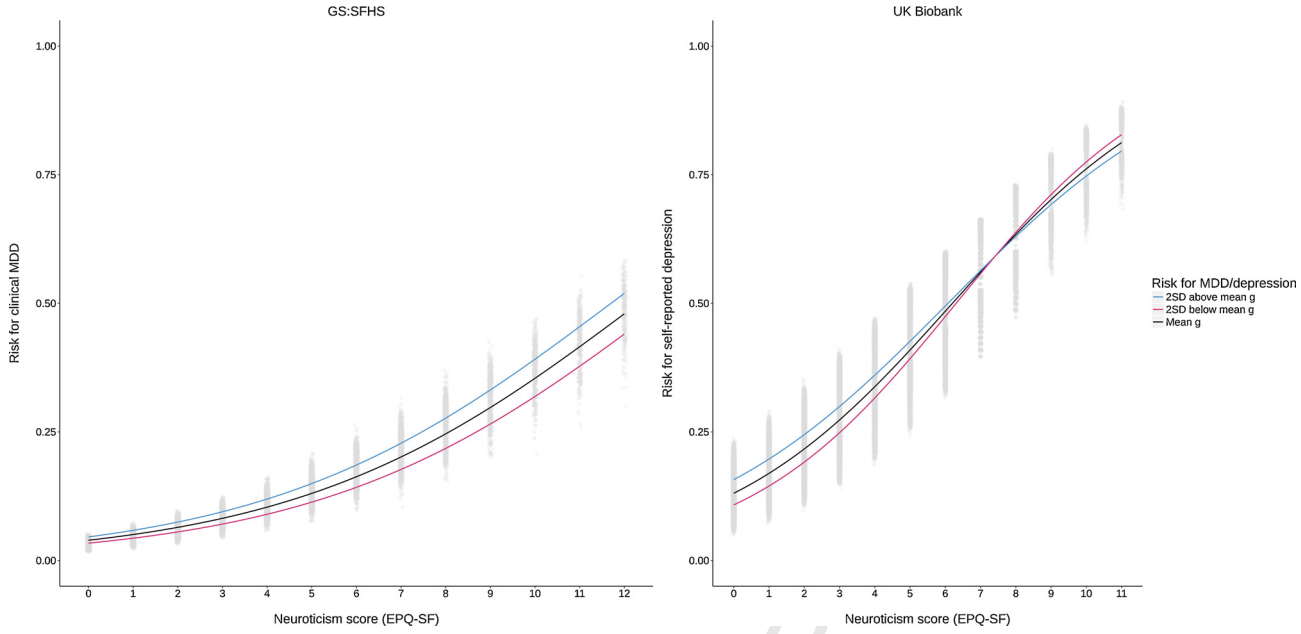

Fig. 1. Predicted risk for MDD and self-reported depression from the interaction of neuroticism and *g* in both GS:SFHS and UK Biobank. Regression lines reflect the interaction at mean *g* (black line) and 2SD above (blue line) and below mean *g* (pink line).

$P < 1.00 \times 10^{-4}$). *g* had no independent effect on risk for MDD (OR = 1.02, 95% CIs = [0.99, 1.07], $P = 0.53$).

3.1.2. Interaction between neuroticism and g on MDD

No interaction was found between neuroticism and *g* (OR = 1.03, 95% CI = [0.98, 1.08], $P = 0.32$), see Fig. 1 and Table 2, even after co-varying for SIMD. However, the main effect of neuroticism was strongly associated with MDD risk (OR = 3.71, 95% CI = [3.37, 4.12], $P < 1.00 \times 10^{-4}$) whilst *g* was associated with a small increase in MDD risk (OR = 1.14, 95% CIs = [1.07, 1.20], $P < 1.00 \times 10^{-4}$). A main effect was found whereby higher deprivation confers risk for MDD (OR = 0.80, 95% CIs = [0.75, 0.86], $P < 1.00 \times 10^{-4}$).

3.1.3. Associations of neuroticism and g with psychological distress

Neuroticism was associated with increased psychological distress; a 1SD increase in neuroticism was associated with an increase in GHQ of β 0.52 (95% CIs = [0.50, 0.53], $P < 1.00 \times 10^{-4}$). A small inverse relationship was found whereby higher *g* was associated with decreased levels of psychological distress ($\beta = -0.08$, 95% CIs = [−0.09, −0.07], $P < 1.00 \times 10^{-4}$).

3.1.4. Interaction between neuroticism and g on psychological distress

A small interaction suggested higher *g* interacts with neuroticism to mitigate neuroticism's detrimental association on GHQ ($\beta = -0.05$, 95% CIs = [−0.06, −0.04], $P < 1.00 \times 10^{-4}$), see Fig. 2 and Table 2. This interaction remained after co-varying for deprivation.

Table 2
Results of a MCMC generalized linear mixed model from GS:SFHS predicting Odds-Ratios of MDD status, beta-coefficients for psychological distress (GHQ), *P*-value, upper and lower 95% confidence intervals and the Deviance Information Criterion AND results of a logistic regression from UK Biobank predicting Odds-Ratios for MDD status, beta-coefficients for psychological distress (PHQ), *P*-value, upper and lower 95% confidence intervals, the Akaike Information Criterion and adjusted R^2 value for the model.

Sample	Outcome	Variables	Odds-Ratio	β	Lower 95% CIs	Upper 95% CIs	*P*-value	DIC	AIC	R^2
GS:SFHS	MDD	Age	1.00	–	0.99	1.01	9.71×10^{-2}	12,561.35	–	–
		Sex (F)	1.71	–	1.48	1.97	$< 1.00 \times 10^{-4}$			
		Neuroticism	3.71	–	3.37	4.12	$< 1.00 \times 10^{-4}$			
		g	1.14	–	1.07	1.20	$< 1.00 \times 10^{-4}$			
		Neuroticism*g	1.03	–	0.98	1.08	0.32			
UK Biobank	MDD	Age	0.98	–	0.99	0.99	$< 2.00 \times 10^{-16}$	–	98,785	–
		Sex (F)	1.34	–	1.32	1.36	$< 2.00 \times 10^{-16}$			
		Neuroticism	2.40	–	2.36	2.44	$< 2.00 \times 10^{-16}$			
		g	1.06	–	1.04	1.07	5.08×10^{-14}			
		Neuroticism*g	0.96	–	0.95	0.98	$< 1.09 \times 10^{-7}$			
GS:SFHS	GHQ	Age	–	0.00	−0.00	0.00	0.59	47,873.87	–	–
		Sex (F)	–	0.04	0.02	0.07	2.63×10^{-3}			
		Neuroticism	–	0.50	0.49	0.52	$< 1.00 \times 10^{-4}$			
		g	–	−0.04	−0.05	−0.03	$< 1.00 \times 10^{-4}$			
		Neuroticism*g	–	−0.05	−0.06	−0.04	$< 1.00 \times 10^{-4}$			
UK Biobank	PHQ	Age	–	−0.02	−0.02	−0.01	$< 2.00 \times 10^{-16}$	–	–	0.2976
		Sex (F)	–	−0.02	−0.02	−0.01	1.57×10^{-8}			
		Neuroticism	–	0.51	0.51	0.52	$< 2.00 \times 10^{-16}$			
		g	–	−0.05	−0.06	−0.05	$< 2.00 \times 10^{-16}$			
		Neuroticism*g	–	−0.02	−0.03	−0.02	$< 2.00 \times 10^{-16}$			

MCMC: Markov Chain Monte Carlo; GS:SFHS: Generation Scotland: the Scottish Family Health Study; GHQ: General Health Questionnaire; DIC: Deviance Information Criterion; *g*: General Intelligence; MDD: major depressive disorder; PHQ: Patient Health Questionnaire; AIC: Akaike Information Criterion.

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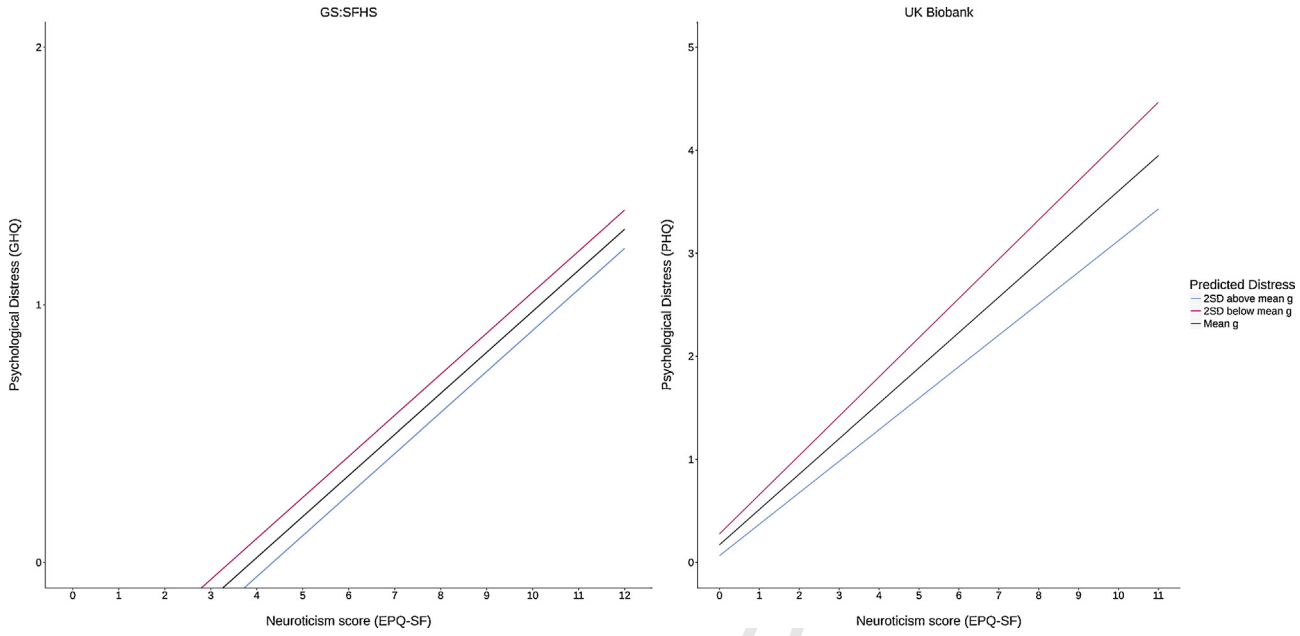

Fig. 2. Psychological distress scores from the interaction of neuroticism and *g* in both GS:SFHS (GHQ) and UK Biobank. Regression lines reflect the interaction at mean *g* (black line) and 2SD above (blue line) and below mean *g* (pink line).

3.2. UK Biobank

As reported in Table 1, MDD cases were younger, predominately female, and had higher psychological distress (PHQ) and neuroticism scores than non-depressed cases. Significant differences were found in verbal-numerical reasoning (in which non-depressed cases performed better) and reaction time (in which depressed cases performed better). *g* was higher in depressed cases ($t(61357) = -2.65$, $P = 8.12 \times 10^{-3}$, Cohen's $d = 0.02$). Non-depressed cases had lower deprivation scores than depressed cases; ($t(57110) = -20.08$, $P = 2.2 \times 10^{-16}$,Cohen's $d = 0.14$), although this difference was small. See the Supplementary materials for full statistical output.

3.2.1. Associations of neuroticism and g with MDD status

Higher neuroticism was associated with increased likelihood of self-reported depression. For every 1SD increase in neuroticism, the odds for depression increased by 2.39 (95% CIs = [2.35, 2.43], $P < 2.00 \times 10^{-16}$). No main effects of *g* were found (OR = 1.00, 95% CIs = [0.99, 1.01], $P = 0.86$). Small effects of age and sex were found.

3.2.2. Interaction between neuroticism and g on MDD

A small interaction was found in which high levels of intelligence and neuroticism associate with reduced self-reported depression (OR = 0.96, 95% CIs = [0.95, 0.98], $P = 1.09 \times 10^{-7}$), see Table 2 and Fig. 1. This interaction remained after co-varying for deprivation.

3.2.3. Associations of neuroticism and g with psychological distress

Neuroticism was moderately associated with increased levels of psychological distress. For every 1SD increase in neuroticism, PHQ increased by β 0.52 (95% confidence intervals = [0.51, 0.52], $P < 2.00 \times 10^{-16}$). *g* was associated with a small reduction in PHQ ($\beta = -0.08$, 95% CIs = [−0.08, −0.07], $P < 2.00 \times 10^{-16}$).

3.2.4. Interaction between neuroticism and g on psychological distress

A small interaction was found in which *g* moderates the detrimental effects of neuroticism on psychological distress ($\beta = -0.02$, 95% CIs = [−0.03, −0.02], $P < 2.00 \times 10^{-16}$), see Table 2 and Fig. 2. This interaction remained after co-varying for deprivation.

4. Discussion

The cross-sectional associations between neuroticism, general intelligence (*g*), MDD, self-reported depression, and psychological distress were examined in two large population based cohorts; GS:SFHS and UK Biobank. Neuroticism was strongly associated with increased risk for both MDD diagnosis and self-reported depression, replicating previous findings [6,7]. Intelligence conferred no consistent independent effects but associated with an increased risk for depression once neuroticism was adjusted for. UK Biobank data suggest an interaction whereby higher *g* has a small effect in reducing the impact of neuroticism on self-reported depression. This interaction was small, both absolutely, and in comparison to the main effects of neuroticism. No such interaction was found in GS:SFHS using a clinical measure of MDD. However, across samples, the risk conferred by neuroticism after co-varying for *g* appears to be increased in terms of the absolute OR value when compared to basic models. Overall, results demonstrate an association whereby intelligence provides modest protection against the risk-conferring effects of neuroticism on self-reported depression, but not clinical MDD.

Consistent and replicable findings were found suggesting higher neuroticism associates with increased psychological distress, whereas higher intelligence associates with reduced psychological distress. A small interaction was found across samples such that lower distress associates with higher intelligence and lower neuroticism. Although these results are of small magnitude, they suggest an important interaction whereby higher *g* lessens the strength of the neuroticism-distress association.

This is the first study of intelligence's potential protective influence on MDD [63], self-reported depression, and psychological distress in high neuroticism individuals. Consistent with previous research the strong link between neuroticism with increased risk for depression and psychological distress was replicated with moderate effect sizes. Although longitudinal work suggests intelligence provides protection to mental health

[24,28,29], we found *g* increased the risk for depression when adjusted for neuroticism. The magnitude of this risk was very small, however. Across cohorts, intelligence associated with decreased levels of psychological distress. A modest association of intelligence as a mitigating factor in reducing psychological distress in individuals with high neuroticism was found in both cohorts. Although this study suggests intelligence provides a protective function in self-reported depression and psychological distress (which mirrors previous research [23,41,42]), intelligence was not found to be protective against diagnosis of depression in those high in neuroticism.

It is unclear why intelligence associates with protection to risk for psychological distress, but not MDD. One supposition is that individuals with higher intelligence may be more likely to seek help, and therefore are more likely to receive a clinical diagnosis of depression. Another postulation could be that intelligence has an effect only during times of depressive episode. A state-dependent association of cognitive ability has been suggested in which variability in intelligence co-varies with depressive episode and remission (for a comprehensive review, see Sackeim and Steif [26]). As such, subsequent investigations may benefit from addressing the same hypotheses examining individuals with current MDD in comparison to individuals in remission, and controls. Increased psychological distress is an established symptom of depression and often used in clinical diagnosis [31,32]. Goldberg [33] described distress as representing the overall severity of depression and so it is likely that individuals scoring highly on measures of psychological distress may be more likely to self-report the disorder, irrespective of its clinical significance. However, we must be mindful of the complexities of causality; whilst it is likely that the neuroticism trait prospectively predicts later distress and self-reported depression, we cannot be certain that these factors are not manifestations of the same underlying risk.

Intelligence could be a marker of system integrity [64] in which increased intelligence circumvents negative mood biasing in individuals high in neuroticism that may lead to distress and disorder [65]. Alternatively, more intelligent individuals may be better able to employ successful coping mechanisms during times of distress: higher intelligence associates with increased resilience to adversity in children [66]. Research suggests that psychosocial factors are associated with resilience to mood disorders [67]. Proactive and psychosocial coping mechanisms may enable individuals decrease transient feelings of distress and to implement established, effective strategies learned from previous exposure to distress or depression [68]. This possibility is consistent with the finding that whereas *g* and neuroticism interacted to associate with reduced psychological distress, the same interaction was not found in clinical MDD. It would be interesting to explore intelligence's influences on coping style [69] and subsequent psychological distress and MDD diagnosis in future investigations. Intelligence may influence the adoption of specific coping strategies, and this could be a mediating factor in the 'depressogenic' process.

Some caveats merit comment. Different cognitive tasks were used to generate *g* across our samples. In GF:SFHS, pre-existing, standardized measures were used, whereas UK Biobank used bespoke cognitive tasks. Further replication utilising standardised measures would be beneficial. A second limitation is the differing MDD phenotypes used in each sample. In GS:SFHS, MDD was determined using a semi-structured interview [47], obtaining a robust MDD phenotype based on a standardised diagnostic tool. In UK Biobank, self-reported questionnaires were aggregated to form a depression phenotype; this data is not as comprehensive. Although it is of benefit to have conducted an independent replication within this study, the disparity in depression phenotypes may explain not only the difference in prevalence rates across samples, but also why an interaction was found in UK Biobank and not GS:SFHS. Thirdly, this investigation only examined neuroticism. Personality represents stable individual dispositions in emotional reactivity, behavioural tendencies, and cognitive styles [22,70], which may be moderated by intelligence in predicting mental health outcomes. Examining such associations between all major dimensions of personality in subsequent research is advised. As neuroticism and MDD share genetic aetiology [2,3], causality cannot be inferred here, although the associations reported do make a significant contribution to the literature. Because neuroticism is a stable trait and MDD is a disease with a given age of onset, we can use neuroticism to predict an individual's risk for depression, without needing to infer causality.

In conclusion, this study fails to demonstrate that intelligence confers protection to clinical MDD in those with high neuroticism. However, in both samples, a modest interaction was found in which higher intelligence appears to ameliorate the detrimental association between neuroticism and psychological distress. It would be useful to determine this relationship prospectively in a sample where incident cases of MDD can be identified. An important corollary of this work may inform risk and resilience mechanisms in MDD. Future studies to disentangle the mechanisms driving depression are an important next step in further elucidating the aetiology of the disorder.

Author contributions

L.N. wrote the manuscript text and prepared all tables and figures. A.M. was the main supervisor for the project, with co-supervision provided by S.R. and S.C. M.J. aided in the statistical analysis. L.N. and E.H. contributed to the data entry for the project. D.K., D.P., I.D., C.G. and D.B. reviewed the manuscript.

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Disclosure of interest

The authors have not supplied their declaration of competing interest. Q3

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2016.12.012.

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