Repeated Low-Grade Infections Predict Antidepressant-Resistant Depression:

A Nationwide Population-Based Cohort Study

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ABSTRACT

Background: The relationship between severe inflammation and clinical depression in the context of major medical illnesses has been addressed, but the relationship between inflammation caused by mild infections and clinical depression is unclear. We aimed to examine whether a history of repeated low-grade infections (RLGI) in medically healthy subjects (MHS) could increase their vulnerability to major depressive disorder (MDD) (*ICD-9-CM*) and whether RLGI could be associated with higher resistance to antidepressants in those developing MDD.

Method: A nationwide, population-based cohort study (January 1996 to December 2011) was conducted for MHS with and without a history of RLGI. The rates of MDD during an up to 8-year follow-up period were compared between the 2 groups in 2 independent cohorts. The stratified responses to adequate antidepressant trials, including easy-to-treat (ETT) and difficult-to-treat (DTT) responses, were also compared in the MDD patients.

Results: During the follow-up, the 2 cohorts consistently revealed that the RLGI(+) (ie, high-inflammation; n = 727) group had a significantly higher chance of developing MDD over time than the RLGI(–) (ie, low-inflammation; n = 443) group: Cox proportional hazards regression models showed that the hazard ratio associated with a history of RLGI was 1.369 to 1.911 ($P < .001$), after adjusting for confounding factors. The RLGI(+) group was consistently associated with a higher likelihood of DTT responses than was the RLGI(–) group (Cohort-2002: 11.5% vs 7.6%; Cohort-2004: 11.8% vs 4.3%; $P < .05$ by Wald χ^2 tests in both cohorts).

Conclusions: This is the first large-scale retrospective cohort study to report a reliable temporal association between a history of RLGI and subsequent diagnosis of MDD and poor responses to antidepressants in 2 independent cohorts. Our data support the view that repeated mild infections play a role in the pathophysiology of MDD and antidepressant-resistant depression.

J Clin Psychiatry 2018;79(1):17m11540

To cite: Jeng J-S, Li C-T, Chen M-H, et al. Repeated low-grade infections predict antidepressant-resistant depression: a nationwide population-based cohort study. *J Clin Psychiatry.* 2018;79(1):17m11540.

To share: https://doi.org/10.4088/JCP.17m11540

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A growing body of evidence supports that inflammation is involved in the pathogenesis of depressive disorders.[1–3] Systemic inflammation in physically ill patients is associated with an increased prevalence of clinical depression. For example, major depressive disorder (MDD) was diagnosed in up to 50% of patients with hepatitis C undergoing prolonged interferon-α (IFN-α) treatment.[4] Likewise, 40%–45% of malignant melanoma patients treated with high-dose IFN-α also developed MDD during the course of therapy.[5,6] Drastic changes in the host's inflammation profile have been linked to the development of adverse outcomes such as depression.

On the other hand, there is evidence to support a link between acute, self-limiting, mild infections and postinfection depressive symptoms in medically healthy subjects (MHS).[7] The mood disturbances following an acute infection are usually adaptive and reversible; yet, in some vulnerable individuals, a more sustained and severe pattern of behavioral and physiological changes characteristic of MDD might develop after a mild infection.[7] Recently, a retrospective cross-sectional study[8] reported that 2 or more acute infections during the previous 12 months were associated with more mental health problems (eg, depression and anxiety) than found in those with 1 or no acute infections. We hypothesize that a past history of repeated low-grade infections (RLGI) could be a risk factor for increased vulnerability to clinical depression in MHS. The pathogenesis of repeated low-grade infections involves the inflammatory process of the host and results in increased secretions of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α).[9,10]

A heightened inflammatory profile is believed to be involved in some of the biological mechanisms associated with depressive disorders and treatment responses.[1–3] A retrospective analysis[11] suggested that elevated levels of inflammation at baseline are contributory to treatment resistance in depressed patients. Recently, a randomized controlled study[12] revealed that the anti-inflammatory drug infliximab, a TNF-α antagonist, could be particularly effective in treatment-resistant depressed patients with increased inflammation before treatment. However, whether RLGI could predict treatment resistance to antidepressants in patients with depression remains elusive.

Clinical Points

- Repeated low-grade infections (RLGI) increased the risk of developing major depressive disorder (MDD) later in life.
- MDD patients with RLGI had the higher likelihood of antidepressant resistance compared with those without RLGI.
- RLGI was a risk factor for development and treatment resistance of MDD.

Therefore, we performed a nationwide, population-based, long-term study and compared the rates of MDD in MHS with and without a history of RLGI in 2 separate cohorts. We aimed to investigate whether a past history of RLGI in MHS was associated with increased risks of developing depression and whether RLGI could be associated with higher resistance to antidepressants in those developing MDD.

METHODS

Data Sources for the Human Study

We used the 1996–2011 Taiwan National Health Insurance Research Database (NHIRD), which contains comprehensive information about clinical visits for each insured subject, including demographic data, dates of visits, diagnostic codes according to the clinical modification of the *ICD-9-CM*, and prescription details. Because the dataset was released for research purposes and included only scrambled information on patient and physician identification, a signature of informed consent was not necessary, and the study was exempt from full-committee review by the local ethics review committee.

Identification of the RLGI(–) and RLGI(+) Groups

Two independent cohorts, Cohort-2002 (N = 78,186) and Cohort-2004 (N = 49,008), were investigated. For these 2 cohorts, the main study groups were all recruited from medically healthy subjects who had evidence of RLGI from January 1996 to December 2011 (Supplementary eFigure 1). Details regarding the selection of the groups are available in the supplementary material online. The RLGI consisted of commonly diagnosed upper airway infections. To determine the commonly diagnosed infections or inflammatory conditions, we first investigated the most prevalent diagnoses for which nonsteroidal anti-inflammatories (NSAIDs) were prescribed (for the top 15 diagnoses, please refer to Supplementary eTable 1). In order to be more specific, only the diagnoses involving the upper airway system were then selected.

The main study groups, the RLGI(–) (ie, low-inflammation; n = 39,093 in Cohort-2002; n = 24,504 in Cohort-2004) and RLGI(+) (ie, high-inflammation; n = 39,093 in Cohort-2002; n = 24,504 in Cohort-2004) groups (Supplementary eFigure 1), were identified from the frequency of upper airway infections during 1 year before the start of follow-up (Figure 1A). The high-frequency group (the first one-third) and the low-frequency group (the last one-third) were matched in a 1:1 ratio for sex, age (≤ 50 years), premium ratable wage, and a score of 0 on the Charlson Comorbidity Index (CCI)[14] (Supplementary eFigure 1). Inclusion of subjects with a CCI score of 0 at enrollment was used to ensure the subjects were medically healthy without major or chronic medical conditions.[13,14]

Outcome Measures for Cases Developing MDD

We compared the incidence of MDD among the inflammation groups, ie, the RLGI(–) vs RLGI(+) group, from 2002 to 2011 (Cohort-2002) and from 2004 to 2011 (Cohort-2004), respectively (Figure 1A), using criteria identical to those in our previously published articles.[15,16] In short, to ensure the validity of the diagnosis of MDD, we excluded patients whose diagnosis of MDD was not made by psychiatrists and included only those whose *ICD-9-CM* diagnosis was made at least twice by board-certified psychiatrists based on their clinical judgment and diagnostic interview (*ICD-9-CM* codes: 296.2 and 296.3). Only adult patients (ie, aged ≥ 18 years) were included. To prevent the misdiagnosis of MDD, we excluded patients who were diagnosed as having bipolar disorders (*ICD-9-CM* codes: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7 and 296.8) and affective psychosis (*ICD-9-CM* code: 296.9) before the enrollment. In addition, patients in Cohort-2002 would be excluded in Cohort-2004.

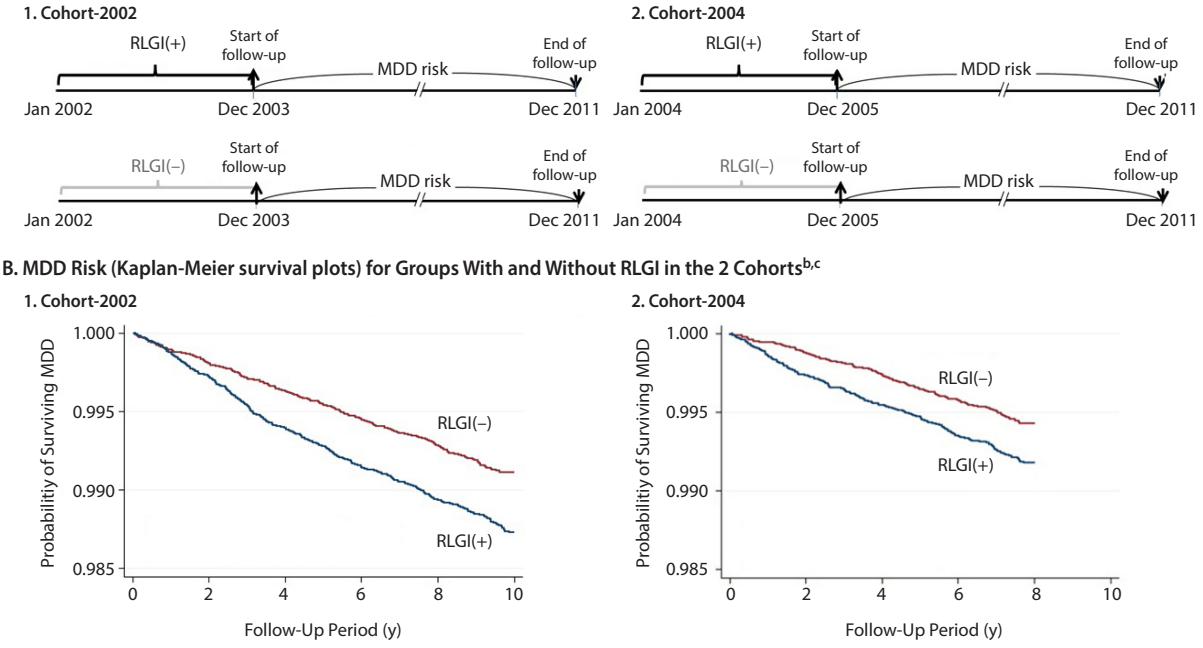
Treatment Outcome Measures in Those Developing MDD

We used the stratification method used in the previous study[15,16] to measure antidepressant responses. In brief, we defined patients as difficult to treat (DTT), intermediately difficult to treat (ITT), and easy to treat (ETT) according to the characteristics of their antidepressant use during a period that extended from 1 year before to 1 year after the first diagnosis of MDD. The adopted criteria for classifying patients into different groups of treatment outcome are widely accepted and have been validated.[15,16] MDD is usually considered as treatment-resistant depression when at least 2 adequate trials with different antidepressants fail to achieve a significant clinical improvement,[17] although varying degrees of treatment refractoriness exist.[18] Therefore, patients were defined as DTT here if 2 or more antidepressant trials were prescribed at an adequate dosage (for example, fluoxetine ≥ 20 mg/d) and duration (≥ 60 consecutive days) during the 2-year period. In contrast, ETT patients were those who took no antidepressants or remained on a single antidepressant. Patients who changed their antidepressants only once were defined as ITT.

Statistical Analysis

The SAS (SAS System for Windows, version 9.2; SAS Institute, Cary, North Carolina) and SPSS (SPSS for Windows, version 21.0, SPSS Inc, Chicago, Illinois) statistical packages were used to analyze the data. Independent *t* test and Pearson χ^2 tests were used to compare the continuous and categorical variables among groups, respectively. Kaplan-Meier survival analysis was used to estimate MDD-free survival curves

Figure 1. Repeated Low-Grade Infections (RLGI) Were Associated With High Risks to Developing a Diagnosis of Major Depressive Disorder (MDD) Over Time



[a]Schematic diagram showing the 2 study groups among the high-inflammation, ie, RLGI(+), and low-inflammation, ie, RLGI(–), groups from 2002 to 2011 (Cohort-2002) and 2004 to 2011(Cohort-2004) selected from among 1 million representatives in the Taiwan National Health Insurance Research Database.
[b]Results consistently showed that a history of RLGI increased MDD risks over time.
[c]Log rank tests were used to compare the between-group survival distributions and a value of $P < .05$ was considered statistically significant.
Abbreviations: RLGI(–) = repeated low-grade infections with low inflammation, RLGI(+) = RLGI with high inflammation.

between the inflammation groups, ie, the RLGI(–) vs RLGI(+) group, respectively. The Kaplan-Meier analysis allowed estimation of survival over time even when subjects followed for different lengths of time were dropped during follow-up. The relationships between a history of RLGI at baseline and the subsequent development of MDD (from 2004 to 2011) were examined using Cox proportional hazards (Cox PH) regression models with adjustment for other factors (eg, age, sex, and income levels at baseline), respectively, in 2 cohorts. All assumptions for the Cox PH models were tested and met. Hazard ratios (HRs, as a measure of effect size) and their 95% confidence intervals (CI) were all reported. Log rank tests were used to compare the between-group survival distributions. Wald χ^2 tests were used to study for association between antidepressant responses (ie, ETT, ITT, and DTT) and the RLGI groups. Significance was set at a P value less than .05.

RESULTS

Demographic and Clinical Variables Between Inflammation Groups

The RLGI(–) and RLGI(+) groups were well matched for age, sex, CCI = 0, and distribution of income levels in Cohort-2002 and Cohort-2004 (Table 1). For both cohorts, the RLGI(+) group had a significantly higher frequency of low-grade infections at baseline than the RLGI(–) group ($P < .001$). During the follow-up period, the RLGI(+) group had a greater chance of being diagnosed with MDD over time than the RLGI(–) group in both cohorts (Figure 1B, left and right). There was no difference in the time to develop a diagnosis of MDD between the 2 groups in the 2 cohorts. In Cohort-2002, the mean (SD) duration to development of MDD was 4.51 (2.83) years in the RLGI(+) group and 4.42 (2.76) years in the RLGI(–) group. In Cohort-2004, the duration was 3.58 (2.38) and 3.30 (2.13) years in the RLGI(+) and RLGI(–) groups, respectively.

Correlation Between RLGI and Risk of Depression

The Cox PH regression model showed that the HRs associated with the history of RLGI were 1.369 in Cohort-2002 and 1.911 in Cohort-2004 ($P < .001$), after adjustments for age, sex, and baseline income levels (Table 2). The results implicated the history of RLGI as an independent factor that increases MDD risks directly. Women had a 1.745- to 1.892-fold increase in HR of developing MDD than men ($P < .001$). In Cohort-2002, higher income at baseline was a protective factor, since the MDD HRs associated with baseline income levels (low income was used as a reference) were 0.722 (0.608 to 0.858, $P < .001$) for medium income and 0.690 for high income (0.567 to 0.839, $P < .001$), after adjusting other covariates. The results in Cohort-2004 were similar to those in Cohort-2002, favoring a higher income at baseline as a protective factor (Table 2).

Table 1. Demographic Data and Clinical Variables

Variable	Cohort-2002 RLGI(−) (n = 39,093)	Cohort-2002 RLGI(+) (n = 39,093)	*P* Value	Cohort-2004 RLGI(−) (n = 24,504)	Cohort-2004 RLGI(+) (n = 24,504)	*P* Value
Baseline variables[a]						
Age, mean (SD), y	32.72 (9.19)	32.72 (9.19)	.989	32.42 (9.11)	31.85 (9.11)	.990
Sex (male), n (%)	17,451 (44.6)	17,451 (44.6)	> .999	10,687 (43.6)	10,687 (43.6)	> .999
CCI score (at baseline), mean (SD)	0.00 (0.00)	0.00 (0.00)	> .999	0.00 (0.00)	0.00 (0.00)	> .999
Income group (at baseline), n (%)			> .999			> .999
Low	17,536 (44.9)	17,536 (44.9)		10,244 (41.8)	10,244 (41.8)	
Medium	12,260 (31.4)	12,260 (31.4)		7,946 (32.4)	7,946 (32.4)	
High	9,297 (23.8)	9,297 (23.8)		6,314 (25.8)	6,314 (25.8)	
No. of low-grade infections, mean (SD)						
With NSAID prescription, times/y	0.76 (0.29)	5.56 (3.68)	< .001*	0.72 (0.26)	5.00 (3.27)	< .001*
Total,[b] times/y	1.45 (1.41)	7.32 (4.80)	< .001*	1.33 (1.27)	6.59 (4.39)	< .001*

[a]Matching variables. [b]A diagnosis of low-grade infection in combination with or without prescription of an NSAID.
*$P < .05$.
Abbreviations: CCI = Charlson Comorbidity Index, NSAID = nonsteroidal anti-inflammatory.

Antidepressant Responses and a Positive History of RLGI

We divided MDD patients into 3 groups according to their antidepressant use patterns in each of the cohorts. As shown in Table 3, in Cohort-2002, 75.9% of the depressed patients without a history of RLGI [the RLGI(−) group] were relatively easy to treat with antidepressants [ie, ETT in RLGI(−) in Table 3]. In Cohort-2004, 83.5% of the depressed patients in the RLGI(−) group were classified as ETT, which was consistent with Cohort-2002. These patients were relatively easy to treat since they did not undergo antidepressant treatment or were treated with only one type of antidepressant. However, approximately 11.5% and 11.8% of the depressed patients with a positive history of RLGI in Cohort-2002 and in Cohort-2004, respectively, showed higher resistance to antidepressants [ie, DTT in RLGI(+) in Table 3], since they failed to respond to adequate antidepressant trials 2 or more times in the index period. The antidepressant responses were significantly different between the RLGI(+) and RLGI(−) groups in both Cohort-2002 and Cohort-2004 (all $P < .05$, Table 3). The association analyses consistently revealed that the RLGI(+) group was associated with a higher likelihood of DTT than the RLGI(−) group in the 2 cohorts (all *P* values < .05, Table 3).

Table 2. Adjusted Hazard Ratio (HR) From Cox Proportional Hazards Regression Model Predicting a Diagnosis of Major Depressive Disorder During Follow-Up in 2 Independent Cohorts[a]

Variables	Cohort-2002 HR	Cohort-2002 95% CI[b]	Cohort-2002 *P* Value	Cohort-2004 HR	Cohort-2004 95% CI[b]	Cohort-2004 *P* Value
Inflammation [RLGI(+)]	1.369	1.189–1.576	< .001*	1.911	1.528–2.391	< .001*
Age	1.000	0.992–1.008	.967	0.999	0.986–1.012	.864
Sex (female)	1.892	1.626–2.202	< .001*	1.745	1.387–2.194	< .001*
Income at baseline						
Medium vs low	0.722	0.608–0.858	< .001*	0.674	0.516–0.880	.004*
High vs low	0.690	0.567–0.839	< .001*	0.631	0.468–0.852	.003*

[a]Interaction between the factors inflammation × income was nonsignificant (Wald statistic = 3.560, $P = .169$).
[b]Lower to upper bound.
*$P < .05$.
Abbreviation: RLGI(+) = repeated low-grade infections with high inflammation.

DISCUSSION

The present study was the first to reveal a reliable temporal relationship between a history of RLGI and an increased vulnerability to depression. Furthermore, we found that a history of RLGI was significantly associated with worse responses to antidepressants. Supporting evidence included the enhanced MDD risk in the RLGI(+) group versus the RLGI(−) group (Figure 1B, left and right), and the enhanced risk of difficult-to-treat MDD in the RLGI(+) group versus the RLGI(−) group in the 2 independent cohorts (Table 3). The HR associated with the history of RLGI was 1.369 to 1.911 (Table 2).

The strength of the present study is that data were gleaned from the NHIRD. First, this large nationwide database is devoid of investigator bias in judging depressive symptoms, and it provided a more objective investigation of the effects of RLGI on depression. Since nearly 99% of Taiwanese inhabitants are covered by the national health insurance plans, all known medical conditions over time are recorded. Second, all diagnoses of MDD were verified by specialists.

Our findings were in line with a cross-sectional study[8] of 10th graders in Norway, which revealed a significant association between a retrospective report of 2 or more acute infections during the previous 12 months and psychiatric symptoms. The present study provided more direct support for the RLGI-depression association. A link between acute, self-limiting, mild infections and postinfective depressive symptoms has been identified.[7] Multiple infective agents, including both viral and bacterial pathogens, are able to trigger short-term depression for a period following infections.[19] Reasonably, repeated infections activate the immune system and increase the proinflammatory cytokines, further disturbing the physical homeostasis.[20] Our results extend the RLGI-depression link from depressive symptoms to a clinical diagnosis of MDD in human subjects. The etiologic link between low-grade infection/inflammation and depression tends to involve multiple processes, such

Table 3. Depression Treatment Outcome Between the RLGI(+) and RLGI(–) Group in 2 Cohorts[a]

	Cohort-2002 (years 2003–2011)				Cohort-2004 (years 2005–2011)			
MDD During the Follow-Up	RLGI(–) (n = 328)	RLGI(+) (n = 489)	*P* Value[b]	*P* Value[c]	RLGI(–) (n = 115)	RLGI(+) (n = 238)	*P* Value[b]	*P* Value[c]
Antidepressant responses			.029*	.009*			.004*	.001*
Easy-to-treat	249 (75.9)	330 (67.5)			96 (83.5)	160 (67.2)		
Intermediately difficult-to-treat	54 (16.5)	103 (21.1)			14 (12.2)	50 (21.0)		
Difficult-to-treat	25 (7.6)	56 (11.5)			5 (4.3)	28 (11.8)		

[a]Values are n (%). [b]By Pearson χ^2 tests. [c]By Wald χ^2 tests.
*$P < .05$.
Abbreviations: MDD = major depressive disorder, RLGI(–) = repeated low-grade infections with low inflammation, RLGI(+) = RLGI with high inflammation.

as the sensitization of corticotropin-releasing factors and stress response pathways.[7] An exaggerated stress response axis also was shown to be involved in the pathophysiology of depression that emerged in the context of IFN-α therapy.[1,21] It has been found that the enhanced response of the hypothalamic-pituitary-adrenal (HPA) axis to the acute administration of IFN-α reveals a vulnerability to IFN-α–induced depression in patients with malignant melanoma.[21] Corticosterone is a stress-response hormone released by activation of the HPA axis. Inflammation is known to increase circulating corticosterone levels.[22] Serotonin plays a key role in the pathophysiology of depression, and the inflammation-depression link involves the activation of indoleamine 2,3-dioxygenase (IDO) and the attenuation of the serotonin precursor tryptophan.[23,24] IDO and its hepatic equivalent tryptophan 2,3-dioxygenase (TDO) oxygenate tryptophan to kynurenine,[25] which reduces the amount of tryptophan available for conversion to serotonin. The decrease in serotonin induces the tryptophan catabolite pathway, which is depressogenic.[24] Our results are consistent with the findings of patients suffering from severe systemic inflammation and also extend the association of the vulnerability to RLGI-related major depression in medically healthy individuals.

Depression comprises a heterogeneous group, and many patients with MDD failed to respond to antidepressants. It has been a belief that a heightened inflammatory profile is a contributor to treatment-resistant depression, and our results directly support this idea. Research specifically focusing on inflammatory cytokines between refractory and nonrefractory depression is scarce. For example, O'Brien et al[26] found that depressed patients who failed to respond to a selective serotonin reuptake inhibitor had significantly higher levels of the proinflammatory cytokines IL-6 and TNF-α compared with healthy controls. A recent clinical research study[12] indicated that infliximab, a TNF-α antagonist, was particularly effective in treatment-resistant depressed patients with increased inflammation before treatment. Our study provided population-based evidence that RLGI is associated with antidepressant-resistant depression.

There are some limitations in this study. First, the incidence of MDD may be underestimated in our study because only those who sought for medical consultation and help would be identified in the NHIRD. However, the diagnosis of MDD was given by board-certified psychiatrists based on their clinical judgment and diagnostic interview, improving the diagnostic validity. Second, patients who had psychiatric diagnoses, including MDD, or who took psychotropic agents may still bear a social stigma in Taiwan. Patients who were in a mild major depressive episode sometimes refused antidepressants, which was classified as ETT in our study. Third, the reported income levels may not be truly correct. For example, people who have high income may try to save taxes or insurance premiums by avoiding full disclosure of their total income. However, income was not a primary factor in our study and was used only as a matching factor to ensure that study groups are comparable. Fourth, the choice to retrospectively survey 1 year before the diagnosis of MDD for RLGI was made to ensure that the medical history was more reliable and available and that our results were more applicable in the clinical settings. However, further studies are warranted to investigate the most optimal time-point for assessing RLGI. Fifth, some information was not available in the NHIRD, such as family history, personal lifestyle, and education. Without these data, we could not assess their impact in our study. Finally, to increase the homogeneity of the study population (specificity) without sacrificing the sensitivity, only commonly diagnosed upper airway infections, but not other infections, were selected here to define the low-grade infections. This decision was made after identifying upper airway infections as common infections in a comprehensive analysis of commonly occurring infections (for details, please refer to the supplementary material available online). The simultaneous prescription of NSAIDs with the infections was used as an index for low-grade infections to exclude many minor and self-limiting infections. Whether other infections or causes of inflammation could have similar findings requires further studies to confirm.

CONCLUSIONS

A reliable temporal relationship was consistently revealed between a history of RLGI and an increased vulnerability to the development of MDD in 2 independent cohorts. In addition, a history of RLGI was more likely to be associated with difficult-to-treat responses to antidepressant trials.

Submitted: February 9, 2017; accepted June 15, 2017.

Published online: December 19, 2017.

Potential conflicts of interest: None of the authors has conflicts of interest to declare.

Funding/support: This study was funded by the Taipei Veterans General Hospital (V105D9-003-MY2-2 and V106C-043) and the Ministry of Science and Technology (MOST103-2314-B-075-072-MY3).

Role of the sponsor: The Taipei Veterans General Hospital and the National Science Council had no role in the design and conduct of study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Additional information: Information on the Taiwan National Health Insurance Research Database can be found at http://nhird.nhri.org.tw/en. The data are managed and supervised by the Bureau of National Health Insurance (BNHI). They can be accessed only by local researchers, and utilization of NHI data is allowed only at specific computer sites designated by the BNHI.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Repeated Low-Grade Infections Predict Antidepressant-Resistant Depression: A Nationwide Population-Based Cohort Study

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DOI Number: https://doi.org/10.4088/JCP.17m11540

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1. **eFigure 1** Flowchart Identifying Groups With or Without RLGI
2. **Study Subjects**
   - Identification of Healthy Subjects With a History of RLGI
   - Exclusion of Those With a History of Psychiatric Disorders at Enrollment
   - The RLGI(–) (ie, low-inflammation) and RLGI(+) (ie, high-inflammation) Groups
3. **eTable 1** Top 15 Diagnoses Associated With NSAID Prescriptions in Taiwan

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Study Subjects

IDENTIFICATION OF HEALTHY SUBJECTS WITH A HISTORY OF RLGI

Two study groups (i.e., RLGI(-) and RLGI(+) groups) were recruited from "medically healthy subjects" in Taiwan who had experiences of repeated low-grade infections (RLGI) from January 1996 to December 2011 (Fig. S1), using Taiwan's National Health Insurance Research Database (NHIRD) that contains comprehensive health information on nearly 99% of the Taiwanese population. The RLGI were represented by a group of common mild infections/inflammation base on diagnoses that were mostly associated with prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs) in otherwise healthy subjects under the National Health Insurance (top 15 diagnoses were shown in Table S1). Most of the diagnoses (80.3 %) involved upper airway system [e.g., the top three in Taiwan - acute upper respiratory infections (24.4 %), acute tonsillitis (5.0 %), and acute nasopharyngitis (4.6%)]; some (19.7 %) included unspecific symptoms/disorders involving other systems or body parts [e.g., back (2.8 %), soft tissues (1.7 %), joint (1.2 %), gastrointestinal tract (1.2 %)]. For improved consistency, RLGI in this study were limited to common upper airway infections, including acute respiratory infections, common cold, acute nasopharyngitis, acute tonsillitis, acute bronchitis/bronchiolitis, acute sinusitis, acute pharyngitis, and influenza (ICD-9-CM codes: 460, 461, 462, 463, 464, 465, 466 and 487). To ensure

that the subjects were medically healthy with no severe infections or inflammation during the study period, cases with immune-compromised diseases or severe/chronic inflammatory diseases were excluded, including all forms of cancer (ICD-9-CM codes 140-239), AIDS (042), systemic lupus erythematosus (710), rheumatoid arthritis (714), psoriasis (696), chronic obstructive pulmonary diseases (491-496), and diabetes mellitus (250), and those who had ever been prescribed with NSAIDs for diagnoses other than the pre-defined LGI (Figure S1).

EXCLUSION OF THOSE WITH A HISTORY OF PSYCHIATRIC DISORDERS AT ENROLLMENT

Two independent cohorts (i.e., Cohort-2002 and Cohort-2004) were recruited. Since the primary outcome was to study the prevalence of MDD during the follow-up in adult subjects with or without a history of RLGI, we excluded those who were under age of 18 years and those who were ever diagnosed of psychiatric disorders during 1996 to 2003 in Cohort-2002 and during 1996 to 2005 in Cohort-2004. Those without records of premium ratable wage in 2002 or 2003 for Cohort-2002, or in 2004 or 2005 for Cohort-2004, were also excluded since such information reflected income levels and was used as a group-matching factor (details given in the following paragraph).

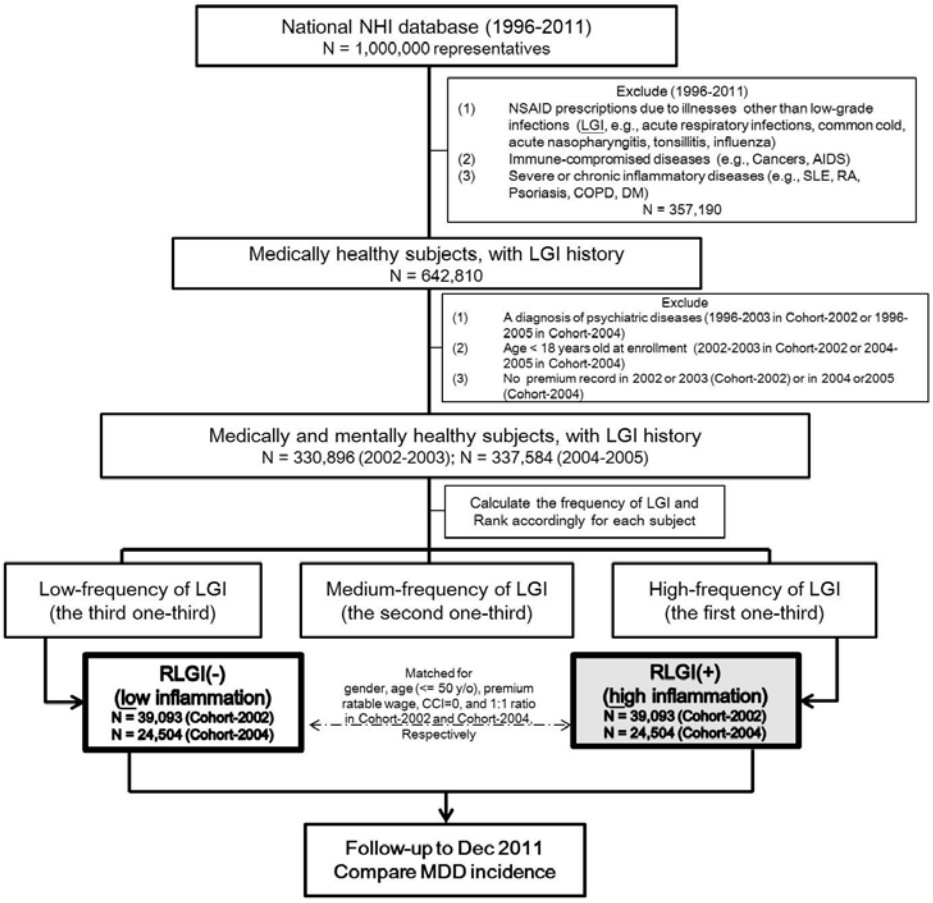
THE RLGI(-)(I.E., LOW-INFLAMMATION) AND RLGI(+)(HIGH-INFLAMMATION) GROUPS

For each subject, we calculated and ranked the frequency of RLGI. The high-, medium-, and low-frequency groups included patients who ranked in the first, second, and last one-third, respectively (Fig. S1). Two main study groups, the RLGI(-)(i.e., low-inflammation) and RLGI(+)(i.e., high-inflammation) groups, were selected from the high- and low-frequency groups, respectively, by matching in a 1:1 ratio for gender, age (<=50 years), premium ratable wage, and a score of zero in the Charlson comorbidity index (CCI) [1]. The CCI is a validated and reliable method in evaluating comorbidity of medical diseases [1, 2], and the CCI score of zero at enrollment was an additional measure to ensure the subjects as medically healthy. It contains 19 disease categories including ulcers, cerebrovascular disease, slight diabetes without complications, diabetes with complications, myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, mild and severe liver disease, conjunctive tissue disease, hemiplegia, renal disease, tumors, leukaemia, lymphoma, malignant tumor, and AIDS, each of which was weighted according to their potential influence on mortality.

Table S1. The top 15 diagnoses associated with NSAIDs prescriptions in Taiwan

NO.	ICD-9-CM codes	% (in all)	% (in top 15)	Diagnosis
1	465	24.4%	39.7%	Acute upper respiratory infections of multiple or unspecified sites
2	463	5.0%	8.1%	Acute tonsillitis
3	460	4.6%	7.5%	Acute nasopharyngitis [common cold]
4	466	4.1%	6.7%	Acute bronchitis and bronchiolitis
5	461	3.3%	5.4%	Acute sinusitis
6	462	3.3%	5.4%	Acute pharyngitis
7	464	2.9%	4.7%	Acute laryngitis and tracheitis
8	724	2.8%	4.6%	Other and unspecified disorders of back
9	784	1.8%	2.9%	Symptoms involving head and neck
10	729	1.7%	2.8%	Other disorders of soft tissues
11	780	1.7%	2.8%	General symptoms
12	715	1.7%	2.8%	Osteoarthrosis and allied disorders
13	487	1.7%	2.8%	Influenza
14	719	1.2%	2.0%	Other and unspecified disorder of joint
15	558	1.2%	2.0%	Other noninfectious gastroenteritis and colitis

Figure S1. A flow chart showing the identifications of groups without or with RLGI. The human study used data from a nationwide database (i.e., 1 million representatives randomly selected from the 23 million beneficiaries from the National Health Insurance Research Database in Taiwan) includes comprehensive health information for more than 99% of Taiwanese residents and is based on health insurance claims. RLGI, Repeated Low-Grade Infections/inflammation; CCI, Charlson comorbidity index.



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