Chronology of Onset of Mental Disorders and Physical Diseases in Mental-Physical Comorbidity - A National Representative Survey of Adolescents

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Abstract

Background

The objective was to estimate temporal associations between mental disorders and physical diseases in adolescents with mental-physical comorbidities.

Methods

This article bases upon weighted data (N = 6483) from the National Comorbidity Survey Adolescent Supplement (participant age: 13–18 years), a nationally representative United States cohort. Onset of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition lifetime mental disorders was assessed with the fully structured World Health Organization Composite International Diagnostic Interview, complemented by parent report. Onset of lifetime medical conditions and doctor-diagnosed diseases was assessed by self-report.

Results

The most substantial temporal associations with onset of mental disorders preceding onset of physical diseases included those between affective disorders and arthritis (hazard ratio (HR) = 3.36, 95%-confidence interval (CI) = 1.95 to 5.77) and diseases of the digestive system (HR = 3.39, CI = 2.30 to 5.00), between anxiety disorders and skin diseases (HR = 1.53, CI = 1.21 to 1.94), and between substance use disorders and seasonal allergies (HR = 0.33, CI = 0.17 to 0.63). The most substantial temporal associations with physical diseases preceding mental disorders included those between heart diseases and anxiety disorders (HR = 1.89, CI = 1.41 to 2.52), epilepsy and eating disorders (HR = 6.27, CI = 1.58 to 24.96), and heart diseases and any mental disorder (HR = 1.39, CI = 1.11 to 1.74).
Conclusions

Findings suggest that mental disorders are antecedent risk factors of certain physical diseases in early life, but also vice versa. Our results expand the relevance of mental disorders beyond mental to physical health care, and vice versa, supporting the concept of a more integrated mental-physical health care approach, and open new starting points for early disease prevention and better treatments, with relevance for various medical disciplines.

Introduction

As the health of young people contributing to future population health and global economic development has been neglected yet, it has now become a 'pressing issue' [1]. The World Health Organization (WHO) and key medical journals such as the *Lancet* are dealing with the challenges that non-communicable diseases and mental disorders are imposing on the health care systems, and it has been claimed that these conditions need to be considered in global efforts in improvements of health, social policy, and health-care delivery [2–4].

The relevance of the integration of mental and physical health arises from adult studies documenting the systematic co-occurrence of mental disorders and physical diseases [3, 5–10]. Findings from longitudinal studies suggest that depression may be a risk factor for the development of cardiovascular diseases such as high blood pressure and coronary heart disease [11–13], autoimmune diseases such as type 1 diabetes, Crohn’s disease, and psoriasis [14], asthma, back pain, and migraines [12]. Temporal associations between depression and rheumatoid arthritis as well as respiratory diseases seem to be bidirectional [12, 15, 16]. Furthermore, post-traumatic stress disorder has been found to precede coronary heart disease [17], type II diabetes [18], and respiratory diseases [19], whereas irritable bowel syndrome may be an antecedent risk factor of epilepsy [20]. The healthcare significance of mental-physical comorbidity is underlined by diminished quality of life and unfavorable course of disease [21], substantial healthcare costs, higher treatment demand, longer treatment duration, and impaired treatment response in persons with mental-physical comorbidity [22, 23]. Integrating mental and physical health has gained attention and advanced into the focus of major journals, current strategic research goals and task forces [24–26].

Despite this relevance, the understanding of mental-physical comorbidity in children and adolescents is scarce, even though some studies support a relationship between mental disorders and physical diseases already during childhood or adolescence [27–35]. First evidence from longitudinal studies suggests that epilepsy may be a risk factor for the development of attention-deficit/hyperactivity disorder [36], that asthma may precede affective and anxiety disorders [37, 38], and that eating disorders may be an antecedent risk factor of a variety of physical diseases [31]. These studies, however, mostly used clinical samples and focused on selected mental or physical problems, and it has been suggested to further develop the life course perspective [39].

The current understanding of the etiology of mental-physical comorbidity is largely based on theoretical models attempting to explain how mental disorders and physical diseases come to be comorbid. These theories suppose that one condition operates as risk factor for the other, or that shared risk factors underlie both mental disorders and physical diseases [5, 40]. However, studies providing implications regarding trajectories in the development of mental-physical comorbidity are lacking. Therefore, knowledge on the temporal course of conditions has been claimed as highly relevant [41, 42].
To better understand the developmental trajectories of mental-physical comorbidity, the main objective of this study was to estimate in adolescents with mental-physical comorbidity the temporal association of mental disorders and physical diseases, using data on the age of onset of a wide range of mental and physical morbidities from a representative national cohort study.

Methods

Study sample

We based this study on data of the National Comorbidity Survey Replication Adolescent Supplement (NCS-A), a national representative survey of initially 10148 United States (US) adolescents (ages 13–18), of which 10123 were students at the time of the survey. Data collection took place between February 2001 and January 2004 [43–45]. Further details on the study protocol of the NCS-A have been described previously [34, 43, 44, 46]. We based our analyses on a subsample of 6483 NCS-A participants for which parents or guardians completed a Self Administered Questionnaire (SAQ), as described previously [34]. Details on the subsample for which no parent report was available, and differences between these two subsamples, are available in supplementary Table 1 of a previous publication that was based on the same dataset [35]. Adolescent and parent provided written informed consent, and the study protocol was approved by the Human Subjects Committee of Harvard Medical School and the University of Michigan.

Diagnostic Assessment

Mental disorders. To assess lifetime mental disorders, trained interviewers administered a computer-assisted version of the WHO Composite International Diagnostic Interview (CIDI) Version 3.0 [45, 46]; details have been described previously [43, 47]. Additional information on adolescents’ mental health was collected from parents or guardians based on the SAQ focusing on attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, major depressive disorder, and dysthymic disorder, because collecting information from parents about those disorders has been found to be diagnostically valuable [48–50]. Information from adolescents and parents was combined. A mental disorder was considered present when diagnostic criteria were met either based on information obtained from adolescent or parent, and, in case of discrepancies, the earlier age was used as age of onset.

We grouped specific mental disorders into the following disorder categories: Any affective disorder (major depressive disorder, dysthymia, and bipolar I or II disorder), any anxiety disorder (agoraphobia, generalized anxiety disorder, social phobia, specific phobia, panic disorder, posttraumatic stress disorder, and separation anxiety disorder), any behavior disorder (attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder), any substance use disorder (alcohol abuse or dependency and drug abuse or dependency), any eating disorder (anorexia nervosa, bulimia nervosa, and binge eating disorder). If an adolescent, based on either adolescent or parent report, fulfilled diagnostic criteria for more than one disorder with a certain disorder category, we used the earliest age as age of onset of the respective disorder category.

Physical diseases. The lifetime presence (’yes’, ’no’) and the age of onset of physical diseases were assessed solely with adolescent self-report, based on a checklist on chronic conditions, which has been applied in the US National Health Interview Survey in similar form [51]. Checklists have been extensively used in national studies [51–54]. It has been shown that children are able to reliably and validly report on their health already at early life stages [55–57]. In this respect, self-report and medical records show good concordance [58], with checklists...
being superior to data obtained from routine data sources in terms of completeness and accuracy [59].

Physical diseases included in our study can be seen in Figs 1 and 2, and further details have been described previously [34].

Table 1. Sociodemographic characteristics of the study sample* (N = 6483).

| Sociodemographic factor | Category               | n   | Weighted % |
|------------------------|------------------------|-----|------------|
| Sex                    | Female                 | 3333| 48.76      |
|                        | Male                   | 3150| 51.24      |
| Age                    | 13–14 y                | 2611| 35.92      |
|                        | 15–16 y                | 2528| 41.88      |
|                        | 17–18 y                | 1344| 22.20      |
| Race                   | Hispanic               | 758 | 14.38      |
|                        | Afro-American          | 1097| 15.07      |
|                        | Other                  | 371 | 4.99       |
|                        | Caucasian              | 4257| 65.55      |
| Parental education     | Less than high school  | 746 | 12.32      |
|                        | High school            | 1852| 29.33      |
|                        | Some college           | 1364| 21.31      |
|                        | College grad           | 2521| 37.04      |
| Poverty index ratio**  | 1.5 (poor)             | 925 | 14.59      |
|                        | 3                      | 1218| 19.26      |
|                        | 6                      | 2139| 32.65      |
|                        | >6                     | 2201| 33.51      |
| Region                 | Northeast              | 1273| 18.15      |
|                        | Midwest                | 2081| 32.27      |
|                        | South                  | 2100| 32.02      |
|                        | West                   | 1029| 15.61      |
| Urbanicity†            | Metropolitan area      | 2645| 40.68      |
|                        | Other urban area       | 2242| 39.48      |
|                        | Rural area             | 1596| 24.42      |
| Number of biological parents living with the adolescent | 0   | 528 | 8.86 |
|                        | 1                      | 2284| 36.46      |
|                        | 2                      | 3671| 56.46      |
| Birth order            | Oldest                 | 2314| 38.81      |
|                        | Youngest               | 1947| 32.42      |
|                        | Others                 | 2222| 32.77      |
| Number of siblings     | 0                      | 323 | 5.24       |
|                        | 1                      | 1853| 29.30      |
|                        | 2                      | 1745| 27.44      |
|                        | 3 or more              | 2562| 38.02      |

Abbreviations: y, years

*Subsample of the National Comorbidity Survey-Adolescent Supplement (NCS-A) including all participants providing self- and parent-reported information on mental disorders.

**Poverty index ratio: The ratio of family income to the poverty threshold of the family, for which the poverty threshold depends on family size [62].

†Urbanicity was categorized based on the classification criteria of the US Census Bureau of 2000: ‘Metropolitan’ corresponds to 1000 or more people per square mile, ‘Other urban area’ corresponds to at least 500 people per square mile, ‘Rural area’ corresponds to other regions [64].

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Statistical analyses

We used weighted data in all statistical analyses, which were conducted with STATA/MP 11 (Stata Corporation, College Station, Texas). Weights were provided with the NCS-A dataset, and had been calculated based on a wide range of sociodemographic variables with regard to [43, 44] to ensure representativeness of the NCS-A study sample with the US adolescent population. We estimated temporal relationships between mental disorders and physical diseases by calculating separate discrete-time proportional hazard models with a non-parametric baseline hazard function using complementary log-log regression, with one of the major classes of mental disorders or ‘any mental disorder’ and one physical disease or ‘any physical disease’ defined as outcome and as time-varying predictor, respectively, and vice versa [60]. We present hazard ratios and their 95% confidence intervals. If diagnostic criteria for more than one mental

![Fig 1. Adjusted discrete-time proportional hazard models estimating the temporal associations of mental disorders predicting subsequent physical diseases.](image-url)

Note: We based our analyses on completer sample sizes* of the total study sample (N = 6483), and adjusted for sociodemographic variables shown in Table 1. The strength of the associations (hazard ratios (HR)) is illustrated by the circle diameter, given in the circles, and 95% confidence intervals, given below the circles. Blue color of the circle (and HRs provided in small standard type font) represent p<0.05 in the total study sample; orange color of the circle and HRs provided in medium-sized bold type font represent p<0.05 in the total study sample and in less than two independent subsamples; red color of the circle and HRs provided in large bold and italic type font represent p<0.05 in the total study sample and in at least two independent subsamples. * Due to missing information on physical diseases from adolescent self-report, sizes of the completer samples are as follows: arthritis: n = 6473, seasonal allergy: n = 6475, skin disease: n = 6479, heart disease: n = 6481, asthma: n = 6477, diabetes/high blood sugar: n = 6481, disease of the digestive system: n = 6481, epilepsy or seizures: n = 6481, any physical disease: n = 6469.

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disorder were fulfilled within a mental disorder class, we used the age of onset of the first mental disorder in this class as age of onset of the total class. As we had to deal with complex survey data, we applied the Taylor series linearization method. In accordance with previous studies [61, 62], we included sociodemographic variables shown in Table 1 in our analyses to control for potential confounding. Adjusted results are presented. To account for the large number of pairwise test, we used an internal subsampling strategy, as previously described [34, 63].

For a low number of subjects information on physical diseases from adolescent self-report was missing. We restricted each analysis to subjects with complete data (see Figs 1 and 2 for completer sample sizes according to each physical disease category). We defined statistical significance at 0.05 and two-sided tests were applied.

Fig 2. Adjusted discrete-time proportional hazard models estimating the temporal associations of physical diseases predicting subsequent mental disorders. Note: We based our analyses on completer sample sizes * of the total study sample (N = 6483), and adjusted for sociodemographic variables shown in Table 1. The strength of the associations (hazard ratios (HR) is illustrated by the circle diameter, given in the circles, with 95% confidence intervals, given below the circles). Blue color of the circle (and HRs provided in small standard type font) represent p > 0.05 in the total study sample; orange color of the circle and HRs provided in medium-sized bold type font represent p<0.05 in the total study sample and in less than two independent subsamples; red color of the circle and HRs provided in large bold and italic type font represent p<0.05 in the total study sample and in at least two independent subsamples. * Due to missing information on physical diseases from adolescent self-report, sizes of the completer samples are as follows: arthritis: n = 6473, seasonal allergy: n = 6475, skin disease: n = 6479, heart disease: n = 6481, asthma: n = 6477, diabetes/high blood sugar: n = 6481, disease of the digestive system: n = 6481, epilepsy or seizures: n = 6481.

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Results

Study cohort descriptives

Table 1 summarizes the study cohort’s sociodemographic characteristics (N = 6483).

Temporal prediction of physical diseases by mental disorders

Results of the adjusted discrete-time proportional hazard models estimating the temporal associations between physical diseases and mental disorders, with mental disorders preceding physical diseases, in the total sample are presented in Fig 1 (results from subsamples available on request). The most substantial associations included those of affective disorders with arthritis and diseases of the digestive system, between anxiety disorders and skin diseases, and between substance use disorders and seasonal allergies. In support of transparency, results of the crude regression models are presented in S1 Table.

Temporal prediction of mental disorders by physical diseases

2 presents results of the adjusted discrete-time proportional hazard models of the associations between mental disorder classes and physical diseases, with physical diseases preceding mental disorders, in the total sample (results from subsamples available on request). The most substantial associations included those of heart diseases with any mental disorder and anxiety disorders, and between epilepsy and eating disorders. In support of transparency, results of the crude regression models are presented in S2 Table.

We provide information on age of onset intervals between the temporal relations of our most robust findings in S3 Table.

Discussion

This article provides temporal association estimates of lifetime mental disorders and physical diseases, based on data from 6483 adolescents of a nationally representative cohort. The most substantial results indicate that affective disorders are a risk factor of arthritis and diseases of the digestive system, that anxiety disorders are a risk factor of skin diseases, and that substance use disorders are a protective factor of seasonal allergies. Vice versa, heart diseases may indicate a risk of anxiety disorders and any mental disorder, and epilepsy a risk of eating disorders.

Our results contribute to previous findings on mental-physical comorbidity mostly resulting from association studies in clinical or population-based samples in adults and documenting comprising relationships between mental disorders and physical diseases [3, 5, 6], including the comorbidity patterns observed in the present study [65–70]. However, as yet, there has been no evidence suggesting a link between substance use disorders and allergies [71], and even though comorbidity between epilepsy and mental disorders has been described in children [28, 30], epidemiological data on the co-occurrence of epilepsy and eating disorders are lacking.

There is rare evidence from adult intervention trials providing insight into the developmental trajectories of co-occurring mental disorders and physical diseases. A contribution of depression in arthritis is supported by a study demonstrating benefits of improved depression care that extended beyond reduced depressive symptoms and included decreased pain in older adults with arthritis and comorbid depression [72]. That anxiety may precede the onset of skin diseases is elucidated by studies of patients with atopic dermatitis reporting improvement in anxiety levels and skin conditions after psychotherapy [73, 74]. For eating disorders and epilepsy, it has been hypothesized based on case reports, that epilepsy arising from a right hemispheric focus and right frontal intracerebral lesions—with their close relationship to the limbic system—may facilitate the development of eating disorders.
system—could play a role in the development of eating disorders [75, 76]. This view is supported by the emerging importance of antiepileptic drugs in the treatment of eating disorders [77]. Finally, for affective disorders preceding diseases of the digestive system, our findings are in line with positive associations between current depression and subsequent disease activity in adult patients with Crohn’s disease or the development of ulcers in previously ulcer-free subjects [78, 79].

In contrast to findings from meta-analyses of studies in adults [80, 81], our data do not suggest anxiety as a risk factor of heart diseases, which may be due to the young age of subjects, as anxiety-induced pathophysiological processes might take decades to develop. Vice versa, the prognostic relevance of cardiovascular diseases for anxiety disorders is less clear in the adult literature. Even though there is some evidence for increased anxiety levels after myocardial infarction [82–84], prospective data providing pre-infarction information is mostly not available, and studies addressing causality are lacking.

Different biological, behavioral, cognitive, and social pathways mediating the relationships between mental disorders and physical diseases have been proposed, but even though study designs to inform about developmental trajectories have already been applied successfully [85], specific comorbidity patterns remain to be determined [5, 40, 86]. Until then, the available data may help to generate hypotheses on the nature of these pathways.

With regard to depression and arthritis, previous work documents the pain-enhancing potential of brain circuits that may be disturbed in depression [87] and, vice versa, the analgesic effects of antidepressants [88], indicating that depression-related brain networks might contribute to the etiology of arthritis. Further pathway candidates are the immune system and the hypothalamic-pituitary-adrenal (HPA) axis, as local inflammation, followed by a systemic reaction, and inappropriately low secretion of cortisol are typical features of arthritis [89, 90], and disturbances of the immune system and the HPA axis have been described in persons with depression [91, 92].

Regarding depression-related onset of diseases of the digestive system, the pathophysiology of the brain-gut axis, involving the corticotropin-releasing factor system [93] may play a role [94], as experimental and clinical studies have demonstrated that acute and chronic stress have impacts on the gastrointestinal system, being permissive in the development of gut diseases [95].

In terms of potential mechanisms underlying the observed prediction of skin diseases by anxiety disorders, it is of note that psychological stress has not only been associated with atopic dermatitis symptom severity [96], but also with various skin health-relevant immune alterations, including slowed wound healing and augmented induction of inflammatory processes and immunoglobulin E (IgE) production [97, 98]. To date, there is only preliminary evidence on the psychoneuroimmunology of anxiety disorders, suggesting that high levels of anxiety might be associated with impaired cellular immunity and IgE synthesis [99, 100].

The reduced risk of seasonal allergy related to substance use disorders in our study may be a consequence of increased consumption of certain substances, for example alcohol, and related immunological changes [101–103], but such positive consequences should be interpreted with caution as it is well established that substance use disorders are associated with increased risk of morbidity and mortality [104].

Body perception and interoceptive conditioning may contribute to the heart disease-related increased risk of anxiety disorders [105]: Heartbeat sensitivity has been shown to be increased in persons suffering from congenital heart diseases compared to healthy controls [106] and studies using heartbeat perception tasks in anxiety disorders support the notion of higher interoceptive sensitivity towards the heartbeat as etiological factor in anxiety diseases [107]. Changes in neuronal structure and function resulting from epileptic seizures [108], possibly
contribute to the risk of eating disorders related with epilepsy. A systematic review of case reports concluded that although simple changes in appetite and eating behavior occurred with hypothalamic and brain stem lesions, the characteristic psychopathology of eating disorders was associated with right frontal and temporal lobe damage [109]. On a molecular level, it has been documented that 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (HTR2C)-receptor-deficient mice showed disturbed feeding behavior and were prone to spontaneous death from seizures, suggesting that 5-HT2C receptors may play a role in linking eating disorders and epilepsy [110].

Strengths of our study include the large nationally representative sample [43], the broadness of mental disorders and physical diseases included, the use of a fully structured diagnostic interview for the assessment of mental disorders, with good quality criteria [43, 47], and the integration of child and parent information [50]. Good response rate and the minimal amount of missing data make it unlikely that loss of subjects has introduced selection bias. Still, the results of this study should be interpreted in light of several limitations; some have been discussed previously, including self-report measures of physical diseases [34], the cross-sectional design, and the use of retrospective data, involving the risk of recall bias [46, 111]. Specifically, the wording of the questions in the physical diseases checklist in the CIDI (“Did a doctor or other health professional ever tell you that you had any of the following illnesses. . .”) might have led to underestimated values, because to positively answer any of these questions the adolescent must have sought a health professional and recalled the diagnosis.

However, a suitable longitudinal dataset allowing studying the chronology of onset of mental disorders and physical diseases in mental-physical comorbidity patterns is lacking while needed to corroborate our findings. Until then, these findings are important to guide future research by providing hypotheses, not least given the novel probing strategy of the National Comorbidity Surveys that has been shown to increase the accuracy of age of onset reports [112]. Moreover, the young and relatively homogenous age range of NCS-A participants within the peak-onset period of mental disorders [113] diminishes the risk of potential bias by age-related impairment in the recall of age of illness onset [114]. Furthermore, lifetime prevalence estimates (reported by our group for the main categories of mental disorders and for physical diseases in [34] and in [62] for specific mental disorders) and age of onset distributions of mental disorders and physical diseases (see S4 Table) are generally in line with previous findings [115–134]. Still, participants could have been rather young at disease onset that could have occurred a decade or more prior to the assessment. This might have introduced recall bias. However, as already mentioned, previous work demonstrated that children’s self-reports on their health are largely reliable and valid [55–57].

Moreover, according to the risk-factor concept by Kraemer and colleagues [135] and due to the cross-sectional design of the study, the presented findings cannot inform about ‘causal risk factors’ but rather about ‘risk factors’ defined as factors preceding the outcome. Besides the temporal relationship, other aspects suggesting causality [136] may be considered, including the strengths of the relationships, for example those between affective disorders and arthritis, with HRs > 3, the specificity of associations, their mechanistic plausibility as discussed above, as well as evidence from the few intervention trials or consistency with the few prospective studies depicted above. Finally, we restricted our analyses to the main categories of mental disorders and physical diseases instead of focusing on subcategories. This hampered integration of results into the literature but ensured sufficient number of cases for each comorbidity pattern, thereby complying with statistical assumptions.

Given the high lifetime prevalence of some comorbidity patterns [34, 35], the partly substantial temporal relationships between lifetime mental disorders and physical diseases, and the high burden for the individual and health economics [21–23, 66], our findings carry
relevance for psychiatric and medical health care and the roles of psychiatrists and other medical specialists in patient management [26], and they can inform research priorities and guide task forces, health policy plans and medical education [137]. In line with current strategic research goals [24, 25, 138], our results may pave the way to improve diagnostic approaches, prevention and treatment of mental-physical comorbidity, for example by considering that treatment of a mental disorder may have implications for a physical disease, and vice versa [139].

A large body of evidence from the WHO World Mental Health Survey documented that the epidemiology of mental-physical comorbidity in adults is comparable worldwide [5], suggesting that the temporal course of onset of mental disorders and physical diseases in adolescents might as well be similar worldwide. However, generalizability of our findings from an adolescent sample on an adult population might be limited, for instance, due to the increasing influence of lifestyle-related factors across the lifespan and, hence, the rather late onset of certain physical disorders [140–142].

Future studies should, besides surveying longitudinal data, include subclinical manifestations of mental disorders and physical diseases, for example using non-invasive measures of arterial structure and function for heart diseases, that occur before the onset of symptoms, in order to better understand the temporal sequence of the relationships. Additionally, it may be worth scrutinizing the comorbidity of mental and physical conditions with regard to the relevance of age of onset, duration of the conditions, and temporal distance between ages of onset (in future studies). Moreover, randomized-controlled intervention trials in representative populations and animal models would be important to shed light on the causality and underlying biological, psychological and behavioral mechanisms of the relationships between mental disorders and physical diseases that we revealed, to foster the development of interdisciplinary preventive approaches and interventions, including the development of clinical guidelines dealing simultaneously with mental disorders and physical diseases [143].

To the best of our knowledge, this is the first comprehensive study of the temporal association of mental disorders and physical diseases in adolescents with mental-physical comorbidity in a nationally representative survey, based on data from 6483 subjects. The most substantial results indicate that affective disorders may increase the risk of arthritis and diseases of the digestive system, that anxiety disorders may increase the risk of skin diseases, and that substance use disorders may decrease the risk of seasonal allergies. Vice versa, heart diseases may indicate a risk of anxiety disorders and any mental disorder, and epilepsy a risk of eating disorders. The clear temporal relationships between mental disorders and physical diseases for specific comorbidity patterns suggest that certain mental disorders may be risk factors of certain physical diseases at early life stages, and vice versa. These results predominantly expand the relevance of mental disorders in adolescence beyond mental health care to physical health care, and vice versa, supporting the concept of integrative care, and open new starting-points for early disease prevention and better treatments, which is relevant for various medical disciplines.

Supporting Information

S1 Table. Discrete-time proportional hazard models for lifetime mental disorders (time-varying) predicting physical diseases (crude models).
(XLS)

S2 Table. Discrete-time proportional hazard models for lifetime physical diseases (time-varying) predicting mental disorders (crude models).
(XLS)
S3 Table. Age of onset intervals of temporal associations between mental disorders preceding physical diseases and vice versa in participants reporting both conditions. (XLS)

S4 Table. Ages of onset by physical disease/mental disorder category. (XLS)

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Author Contributions

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Funding acquisition: MT.

Investigation: MT ES GM.

Methodology: MT AB GM.

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Software: MT AB GM.

Supervision: MT GM.

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References

1. Mokdad AH, Forouzanfar MH, Daoud F, Mokdad AA, El Bcheraoui C, Moradi-Lakeh M, et al. Global burden of diseases, injuries, and risk factors for young people’s health during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2016; 387(10036):2383–401. doi: 10.1016/S0140-6736(16)00648-6 PMID: 27174305.

2. Beaglehole R, Ebrahim S, Reddy S, Voute J, Leeder S. Prevention of chronic diseases: a call to action. Lancet. 2007; 370(9605):2152–7. Epub 2007/12/08. doi: 10.1016/S0140-6736(07)61700-0 PMID: 18063926.

3. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet. 2007; 370(9590):859–77. Epub 2007/09/07. S0140-6736(07)61238-0 [pii] doi: 10.1016/S0140-6736(07)61238-0 PMID: 17804063.

4. World Health Organization. WHO. Global status report on noncommunicable diseases 2010: description of the global burden of NCDs, their risk factors and determinants. Geneva: World Health Organization; 2011.

5. Von Korff MR, Scott KM, Gureje O. Global perspectives on mental-physical comorbidity in the WHO World Mental Health Surveys. Cambridge University Press; 2009.
6. Iacovides A, Siamoul M. Comorbid mental and somatic disorders: an epidemiological perspective. Curr Opin Psychiatry. 2008; 21(4):417–21. Epub 2008/06/04. doi: 10.1097/YCO.0b013e328303ba42 00001504-200807000-000222 [pii]. PMID: 18520749.

7. Mayer EA, Craske M, Nailibhoff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry. 2001; 62 Suppl 8:28–36; discussion 7. Epub 2002/07/11. PMID: 12108819.

8. Scott KM, Von Korff M, Ornelt J, Zhang MY, Bruffaerts R, Alonso J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry. 2007; 29 (2):123–33. Epub 2007/03/06. S0163-8343(06)00253-2 [pii] doi: 10.1016/j.genhosppsych.2006.12.006 PMID: 17336661; PubMed Central PMCID: PMC1913936.

9. Bruffaerts R, Demyttenaere K, Kessler RC, Tachimori H, Bunting B, Hu C, et al. The associations between preexisting mental disorders and subsequent onset of chronic headaches: a worldwide epidemiologic perspective. J Pain. 2015; 16(1):42–52. doi: 10.1016/j.jpain.2014.10.002 PMID: 25451620.

10. Scott KM, Lim C, Al-Hamzawi A, Alonso J, Bruffaerts R, Calsdes-de-Almeida JM, et al. Association of Mental Disorders With Subsequent Chronic Physical Conditions: World Mental Health Surveys From 17 Countries. JAMA Psychiatry. 2016; 73(2):150–8. doi: 10.1001/jamapsychiatry.2015.2688 PMID: 26719969.

11. Patten SB, Williams JV, Lavorato DH, Campbell NR, Eliasziw M, Campbell TS. Major depression as a risk factor for high blood pressure: epidemiologic evidence from a national longitudinal study. Psychosom Med. 2009; 71(9):273–9. doi: 10.1097/PSY.0b013e3181986e5f PMID: 19196807.

12. Patten SB, Williams JV, Lavorato DH, Modgill G, Jette N, Eliasziw M. Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. Gen Hosp Psychiatry. 2008; 30(5):407–13. doi: 10.1016/j.genhosppsych.2008.05.001 PMID: 18774423.

13. Wu Q, Kling JM. Depression and the Risk of Myocardial Infarction and Coronary Death: A Meta-Analysis of Prospective Cohort Studies. Medicine (Baltimore). 2016; 95(6):e2815. doi: 10.1097/MD. 0000000000002615 PMID: 26671852; PubMed Central PMCID: PMCPMC4753948.

14. Andersson NW, Gustafsson LN, Okkel N, Taha F, Cole SW, Munk-Jorgensen P, et al. Depression and the risk of autoimmune disease: a nationally representative, prospective longitudinal study. Psychol Med. 2015; 45(16):3559–69. doi: 10.1017/S0033291715001488 PMID: 26271451.

15. Goodwin RD, Schechner B, Pena L, Feldman JM, Taha F, Lipsitz JD. A 10-year prospective study of respiratory disease and depression and anxiety in adulthood. Ann Allergy Asthma Immunol. 2014; 113(5):565–70. doi: 10.1016/j.anai.2014.08.003 PMID: 25216970.

16. Rathbun AM, Reed GW, Harrold LR. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. Rheumatology (Oxford). 2013; 52(10):1785–94. doi: 10.1093/rheumatology/kes356 PMID: 23236191.

17. Vaccarino V, Goldberg J, Rooks C, Shah AJ, Veledar E, Faber TL, et al. Post-traumatic stress disorder and incidence of coronary heart disease: a twin study. J Am Coll Cardiol. 2013; 62(11):970–8. doi: 10.1016/j.jacc.2013.04.085 PMID: 23810885; PubMed Central PMCID: PMCPMC3823367.

18. Roberts AL, Agnew-Blais JC, Spiegelman D, Kubzansky LD, Mason SM, Galea S, et al. Posttraumatic stress disorder and incidence of type 2 diabetes mellitus in a sample of women: a 22-year longitudinal study. JAMA Psychiatry. 2015; 72(3):203–10. doi: 10.1001/jamapsychiatry.2014.2632 PMID: 25565410; PubMed Central PMCID: PMCPMC4522929.

19. Kotow R, Bronet EJ, Schechter C, Broihier J, Feder A, Friedman-Jimenez G, et al. Posttraumatic stress disorder and the risk of respiratory problems in World Trade Center responders: longitudinal test of a pathway. Psychosom Med. 2015; 77(4):438–48. doi: 10.1097/PSY.0000000000001799 PMID: 25919367.

20. Chen CH, Lin CL, Kao CH. Irritable Bowel Syndrome Increases the Risk of Epilepsy: A Population-Based Study. Medicine (Baltimore). 2015; 94(36):e1497. doi: 10.1097/MD.0000000000001497 PMID: 26356716; PubMed Central PMCID: PMCPMC4616652.

21. Beutel ME, Schulz H. [Comorbid psychological disorders in patients with chronic somatic diseases]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2011; 54(1):15–21. Epub 2011/01/20. doi: 10.1007/s00103-011-1191-2 PMID: 21246324.

22. Hochlehnert A, Niehoff D, Wild B, Junger J, Herzog W, Lowe B. Psychiatric comorbidity in cardiovascular inpatients: costs, net gain, and length of hospitalization. J Psychosom Res. 2011; 70(2):135–9. Epub 2011/01/26. doi: 10.1016/j.jpsychres.2010.09.010 PMID: 21262415.

23. Lehert T, Konnopka A, Riedel-Heller S, Konig HH. [Health economic aspects of physical-mental comorbidity]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2011; 54(1):120–7. Epub 2011/01/20. doi: 10.1007/s00103-011-1187-8 PMID: 21246337.
24. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, et al. Grand challenges in global mental health. Nature. 2011; 475(7354):27–30. Epub 2011/07/08. doi: 10.1038/475027a PMID: 21734685; PubMed Central PMCID: PMC3173804.

25. Foy JM. Enhancing pediatric mental health care: report from the American Academy of Pediatrics Task Force on Mental Health. Introduction. Pediatrics. 2010; 125 Suppl 3:S69–74. Epub 2010/06/11. doi: 10.1542/peds.2010-0788C PMID: 20519564.

26. Sharpe M. Somatic symptoms: beyond 'medically unexplained'. Br J Psychiatry. 2013; 203:320–1. Epub 2013/11/05. doi: 10.1192/bjp.bp.112.122523 PMID: 24187064.

27. Angel RJ, Angel JL. Physical comorbidty and medical care use in children with emotional problems. Public Health Rep. 1996; 111(2):140–5. Epub 1996/03/01. PMID: 8606912; PubMed Central PMCID: PMC1381720.

28. Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol. 2003; 45(5):292–5. Epub 2003/06/05. PMID: 12729141.

29. Erhart M, Weimann A, Bullinger M, Schulte-Markwort M, Ravens-Sieberer U. [Psychological comorbidity in children and adolescents with chronic somatic diseases]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2011; 54(1):66–74. Epub 2011/01/20. doi: 10.1007/s00103-010-1190-0 PMID: 21246331.

30. Freilinger M, Reisel B, Reiter E, Zelenko M, Hauser E, Seidl R. Behavioral and emotional problems in children with epilepsy. J Child Neurol. 2006; 21(11):939–45. Epub 2006/11/10. PMID: 17092458.

31. Johnson JG, Cohen P, Kasen S, Brook JS. Eating disorders during adolescence and the risk for physical and mental disorders during early adulthood. Arch Gen Psychiatry. 2002; 59(6):545–52. Epub 2002/06/05. PMID: 12044197.

32. Seng JS, Graham-Bermann SA, Clark MK, McCarthy AM, Ronis DL. Posttraumatic stress disorder and physical comorbidity among female children and adolescents: results from service-use data. Pediatrics. 2005; 116(6):e767–76. Epub 2005/12/03. doi: 10.1542/peds.2005-0608 PMID: 16322133.

33. Tsai MC, Lin HK, Lin CH, Fu LS. Prevalence of attention deficit/hyperactivity disorder in pediatric allergic rhinitis: a nationwide population-based study. Allergy Asthma Proc. 2011; 32(6):41–6. Epub 2012/01/10. doi: 10.2500/aap.2011.32.3489 PMID: 22221429.

34. Tegethoff M, Belardi A, Stalujanis E, Meinlschmidt G. Association between mental disorders and physical diseases in adolescents from a nationally representative cohort. Psychosom Med. 2015; 77(3):319–32. doi: 10.1097/PSY.0000000000000151 PMID: 25851547.

35. Tegethoff M, Belardi A, Stalujanis E, Meinlschmidt G. Comorbidity of mental disorders and chronic pain: chronology of onset in adolescents of a national representative cohort. J Pain. 2015; 16(10):1054–64. doi: 10.1016/j.jpain.2015.06.009 PMID: 26168877.

36. Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalsgaard S. Childhood Epilepsy, Febrile Seizures, and Subsequent Risk of ADHD. Pediatrics. 2016; 138(2). doi: 10.1542/peds.2015-4654 PMID: 27412639.

37. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Higher risk of developing major depression and bipolar disorder in later life among adolescents with asthma: a nationwide prospective study. J Psychiatr Res. 2014; 49:25–30. doi: 10.1016/j.jpsychires.2013.10.015 PMID: 24275549.

38. Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, et al. Asthma and panic in young adults: a 20-year prospective community study. Am J Respir Crit Care Med. 2005; 171(11):1224–30. doi: 10.1164/rccm.200412-1669OC PMID: 15764721; PubMed Central PMCID: PMCPMC2718460.

39. Taylor AW, Price K, Gill TK, Adams R, Pilkington R, Carrangis N, et al. Multimorbidity—not just an older person’s issue. Results from an Australian biomedical study. BMC Public Health. 2010; 10:718. Epub 2010/11/26. doi: 10.1186/1471-2458-10-718 PMID: 21092218; PubMed Central PMCID: PMCPMC3001730.

40. Valderas JM, Starfield B, Siibald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009; 7(4):357–63. Epub 2009/07/15. doi: 10.1370/afm.983 PMID: 19597174; PubMed Central PMCID: PMC2713155.

41. Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kossos V, Angermeyer MC, et al. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. Pain. 2007; 129(3):332–42. Epub 2007/03/14. doi: 10.1016/j.pain.2007.01.022 PMID: 17350169.

42. Szegethy E. Psychiatry and Pediatrics: New Necessary Directions to Better Treat Adolescents. J Am Acad Child Adolesc Psychiatry. 2016; 55(5):357–8. doi: 10.1016/j.jaac.2016.02.011 PMID: 27126848.

43. Kessler RC, Avenevoli S, Costello EJ, Green JG, Gruber MJ, Heeringa S, et al. National comorbidity survey replication adolescent supplement (NCS-A): II. Overview and design. J Am Acad Child
Adolesc Psychiatry. 2009; 48(4):380–5. Epub 2009/02/27. doi: 10.1097/CHI.0b013e318199705 S0890-8567(09)60045-9 [pii]. PMID: 19242381; PubMed Central PMCID: PMC2718678.

44. Kessler RC, Avenevoli S, Costello EJ, Green JG, Gruber MJ, Heeringa S, et al. Design and field procedures in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). Int J Methods Psychiatr Res. 2009; 18(2):69–83. Epub 2009/06/10. doi: 10.1002/mpr.279 PMID: 19507169; PubMed Central PMCID: PMC2774712.

45. Kessler RC, Merikangas KR. The National Comorbidity Survey Replication (NCS-R): background and aims. Int J Methods Psychiatr Res. 2004; 13(2):60–8. Epub 2004/08/07. PMID: 15297904.

46. Merikangas K, Avenevoli S, Costello J, Koretz D, Kessler RC. National comorbidity survey replication adolescent supplement (NCS-A): I. Background and measures. J Am Acad Child Adolesc Psychiatry. 2009; 48(4):367–9. Epub 2009/02/27. doi: 10.1097/CHI.0b013e31819996f1 S0890-8567(09)60044-7 [pii]. PMID: 19242382; PubMed Central PMCID: PMC2736858.

47. Kessler RC, Avenevoli S, Green J, Gruber MJ, Geyer M, He Y, et al. National comorbidity survey replication adolescent supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. J Am Acad Child Adolesc Psychiatry. 2009; 48(4):386–99. Epub 2009/03/03. doi: 10.1097/CHI.0b013e31819996f1 S0890-8567(09)60044-7 [pii]. PMID: 19252450.

48. Cantwell DP, Lewinsohn PM, Rohde P, Seeley JR. Correspondence between adolescent report and parent report of psychiatric diagnostic data. J Am Acad Child Adolesc Psychiatry. 1997; 36(5):610–9. Epub 1997/05/01. doi: 10.1097/00004583-199705000-00011 PMID: 9136495.

49. De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. Psychol Bull. 2005; 131(4):483–509. Epub 2005/08/03. doi: 10.1037/0033-2909.131.4.483 PMID: 16006799.

50. Grills AE, Ollendick TH. Issues in parent-child agreement: the case of structured diagnostic interviews. Clin Child Fam Psychol Rev. 2002; 5(1):57–83. Epub 2002/05/08. PMID: 11993545.

51. Schoenborn CA, Adams PF, Schiller JS. Summary health statistics for the U.S. population: National Health Interview Survey, 2000. Vital Health Stat 10. 2003;(214):1–83. Epub 2005/03/25. PMID: 15786609.

52. Buist-Bouwman MA, De Graaf R, Vollebergh WA, Alonso J, Bruffaerts R, Ormel J, et al. Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. Acta Psychiatr Scand. 2006; 113(6):492–500. doi: 10.1111/j.1600-0447.2005.00684.x PMID: 16677226.

53. Merikangas KR, Ames M, Cui L, Stang PE, Ustun TB, Von Korff M, et al. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. Arch Gen Psychiatry. 2007; 64(10):1180–8. doi: 10.1001/archpsyc.64.10.1180 PMID: 17909130; PubMed Central PMCID: PMC2248275.

54. Ormel J, Petukhova M, Chatterji S, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, et al. Disability and treatment of specific mental and physical disorders across the world. Br J Psychiatry. 2008; 192 (5):368–75. doi: 10.1192/bjp.bp.107.039107 PMID: 18450663; PubMed Central PMCID: PMC2681238.

55. Lee JJ, Colman RJ, Mitchell PD, Atmadja ML, Bousvaros A, Lightdale JR. Agreement between patient- and physician-completed Pediatric Ulcerative Colitis Activity Index scores. J Pediatr Gastroenterol Nutr. 2011; 52(6):708–13. doi: 10.1097/MPG.0b013e3182099018 PMID: 21593644.

56. Olson LM, Radecki L, Frintner MP, Weiss KB, Korfmacher J, Siegel RM. At what age can children report dependably on their asthma health status? Pediatrics. 2007; 119(1):e93–102. doi: 10.1542/peds.2005-3211 PMID: 17200264.

57. Riley AW. Evidence that school-age children can self-report on their health. Ambul Pediatr. 2004; 4(4 Suppl):371–6. doi: 10.1367/A03-178R.1 PMID: 15264962.

58. Baumeister H, Kristen L, Bengel J, Harter M. High agreement of self-report and physician-diagnosed somatic conditions yields limited bias in examining mental-physical comorbidity. J Clin Epidemiol. 2010; 63(5):558–65. Epub 2009/12/05. S0895-4356(09)60240-6 [pii]. doi: 10.1016/j.jclinepi.2009.08.009 PMID: 19959329.

59. Knight M, Stewart-Brown S, Fletcher L. Estimating health needs: the impact of a checklist of conditions and quality of life measurement on health information derived from community surveys. J Public Health Med. 2001; 23(3):179–86. Epub 2001/10/05. PMID: 11585189.

60. Willett JB, Singer JD. Discrete-time survival analysis. In: Kaplan D, editor. The SAGE Handbook of Quantitative Methodology for the Social Sciences. Thousand Oaks, London, New Delhi: Sage Publications, Inc.; 2004.

61. Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey...
62. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010; 49(10):980–9. Epub 2010/09/22. doi: 10.1016/j.jaac.2010.05.017 PMID: 20855043; PubMed Central PMCID: PMC2946114.

63. Kessler RC, Ormel J, Petukhova M, McLaughlin KA, Green JG, Russo LJ, et al. Development of lifetime comorbidity in the World Health Organization world mental health surveys. Arch Gen Psychiatry. 2011; 68(1):90–100. Epub 2011/01/05. doi: 10.1001/archgenpsychiatry.2010.180 PMID: 2119968.

64. U.S. Census Bureau. Census 2000 Urban and Rural Classification 2000 [cited June 13, 2014]. Available from: http://www.census.gov/geo/reference/ua/urban-rural-2000.html.

65. He Y, Zhang M, Lin EH, Bruffaerts R, Posada-Villa J, Angermeyer MC, et al. Mental disorders among persons with arthritis: results from the World Mental Health Surveys. Psychol Med. 2008; 38(11):1639–50. Epub 2008/02/27. doi: 10.1017/S0033291707002474 PMID: 18288879; PubMed Central PMCID: PMC2946114.

66. Kessler RC, Ormel J, Demler O, Stang PE. Comorbid mental disorders account for the role impairment of commonly occurring chronic physical disorders: results from the National Comorbidity Survey. J Occup Environ Med. 2003; 45(12):1257–66. Epub 2003/12/11. doi: 10.1097/01.jom.0000100000.70011.bb PMID: 14665811.

67. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ. 1999; 318(7196):1460–7. Epub 1999/05/27. PMID: 10346775; PubMed Central PMCID: PMC1115843.

68. Picardi A, Pasquini P. Toward a biopsychosocial approach to skin diseases. Adv Psychosom Med. 2007; 28:109–26. Epub 2007/08/09. doi: 10.1159/0000106800 PMID: 17643322.

69. Ormel J, Von Korff M, Burger H, Scott K, Demyttenaere K, Huang YQ, et al. Mental disorders among persons with heart disease—results from World Mental Health surveys. Gen Hosp Psychiatry. 2007; 29(4):325–34. Epub 2007/06/27. doi: 10.1016/j.genhosppsych.2007.03.009 PMID: 17591509; PubMed Central PMCID: PMC2048744.

70. Rodic D, Meyer AH, Meinlschmidt G. The association between depressive symptoms and physical diseases in Switzerland: a cross-sectional general population study. Front Public Health. 2015; 3:47. doi: 10.3389/fpubh.2015.00047 PMID: 25853116; PubMed Central PMCID: PMC4370044.

71. Patten SB, Williams JV. Self-reported allergies and their relationship to several Axis I disorders in a community sample. Int J Psychiatry Med. 2007; 37(1):11–26. Epub 2007/08/09. doi: 10.1159/0000106800 PMID: 17643322.

72. Linnet J, Jemec GB. Anxiety level and severity of skin condition predicts outcome of psychotherapy in atopic dermatitis patients. Int J Dermatol. 2001; 40(10):632–6. Epub 2001/12/12. PMID: 11737422.

73. Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. J Consult Clin Psychol. 1995; 63(4):624–35. Epub 1995/08/01. PMID: 7673540.

74. Levine R, Lipson S, Devinsky O. Resolution of eating disorders after right temporal lesions. Epilepsy Behav. 2003; 4(6):781–3. Epub 2003/12/31. PMID: 14698720.

75. McElroy SL, Guerdtjikova AI, Martens B, Keck PE Jr., Pope HG, Hudson JL. Role of antiepileptic drugs in the management of eating disorders. CNS Drugs. 2009; 23(2):139–59. Epub 2009/01/29. doi: 10.2165/00023210-200923020-00004 PMID: 19173373.

76. Levenstein S, Kaplan GA, Smith MW. Psychological predictors of peptic ulcer incidence in the Alameda County Study. J Clin Gastroenterol. 1997; 24(3):140–6. Epub 1997/04/01. PMID: 9179731.

77. Mardini HE, Kip KE, Wilson JW. Crohn’s disease: a two-year prospective study of the association between psychological distress and disease activity. Dig Dis Sci. 2004; 49(3):492–7. Epub 2004/05/14. PMID: 15139504.
80. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010; 56(1):38–46. Epub 2010/07/14. doi: 10.1016/j.jacc.2010.03.034 PMID: 20620715.

81. Thurston RC, Rewak M, Kubzansky LD. An anxious heart: anxiety and the onset of cardiovascular diseases. Prog Cardiovasc Dis. 2013; 55(6):524–37. Epub 2013/04/30. doi: 10.1016/j.pcd.2013.03.007 PMID: 23621962.

82. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. The prevalence and persistence of depression and anxiety following myocardial infarction. Br J Health Psychol. 2002; 7(Pt 1):11–21. Epub 2002/11/05. doi: 10.1348/135910702169321 PMID: 12456714.

83. Bjерkeset O, Nordahl HM, Myklebust A, Holmen J, Dahl AA. Anxiety and depression following myocardial infarction: gender differences in a 5-year prospective study. J Psychosom Res. 2005; 58(2):153–61. Epub 2005/04/12. doi: 10.1016/j.jpsychiores.2004.07.011 PMID: 15820832.

84. Hanssen TA, Nordrehaug JE, Eide GE, Bjelland I, Rokne B. Anxiety and depression after acute myocardial infarction: an 18-month follow-up study with repeated measures and comparison with a reference population. Eur J Cardiovasc Prev Rehabil. 2009; 16(6):651–9. Epub 2009/08/27. doi: 10.1097/HJR.0b013e3282e4206 PMID: 19707149.

85. Goodwin RD, Galea S, Perzanowski M, Jacob F. Impact of allergy treatment on the association between allergies and mood and anxiety in a population sample. Clin Exp Allergy. 2012; 42(12):1765–71. Epub 2012/11/28. doi: 10.1111/j.1365-2222.2012.04042.x PMID: 23181792.

86. Cohen S, Rodriguez MS. Pathways linking affective disturbances and physical disorders. Health Psychol. 1995; 14(5):374–80. Epub 1995/09/01. PMID: 7498107.

87. Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. Prog Brain Res. 2000; 122:245–53. Epub 2000/03/29. PMID: 10737063.

88. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatr Neurol. 2001; 26(1):30–6. Epub 2001/02/24. PMID: 11212591; PubMed Central PMCID: PMC1408040.

89. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001; 344(12):907–16. Epub 2001/03/22. doi: 10.1056/NEJM200103223441207 PMID: 11259725.

90. Straub RH, Cutojo M. Involvement of the hypothalamic—pituitary—adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: viewpoint based on a systemic pathogenetic role. Arthritis Rheum. 2001; 44(3):493–507. Epub 2001/03/27. doi: 10.1002/1529-0131(200103)44:3<493::AID-ANR95>3.0.CO;2-U PMID: 11263762.

91. Raedler TJ. Inflammatory mechanisms in major depressive disorder. Curr Opin Psychiatry. 2011; 24(6):519–25. Epub 2011/09/08. doi: 10.1097/YCO.0b013e32834b9db6 PMID: 21897249.

92. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008; 31(9):464–8. Epub 2008/08/05. doi: 10.1016/j.tins.2008.06.006 PMID: 18675469.

93. Tache Y, Martinez V, Wang L, Million M. CRF1 receptor signaling pathways are involved in stress-related alterations of colonic function and visceral hypersensitivity: implications for irritable bowel syndrome. Br J Pharmacol. 2004; 141(8):1321–30. Epub 2004/04/22. doi: 10.1038/sj.bjp.0705760 PMID: 15100185; PubMed Central PMCID: PMC1574904.

94. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. J Physiol Pharmacol. 2011; 62(6):591–9. Epub 2012/02/09. PMID: 22314561.

95. Gareau MG, Silva MA, Perdue MH. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008; 8(4):274–81. Epub 2008/06/10. PMID: 18537635.

96. Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: an overview. Psychol Psychother. 2001; 74(1):6–16. Epub 2001/01/11. 56219. PMID: 11150933. doi: 56219.

97. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol. 2005; 5(3):243–51. Epub 2005/03/02. doi: 10.1038/nri1571 PMID: 15738954.

98. Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, et al. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol. 2004; 113(6):1051–7. Epub 2004/06/23. doi: 10.1016/j.jaci.2004.03.032 PMID: 15208584.

99. Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. Hum Psychopharmacol. 2012; 27(1):6–14. Epub 2012/01/04. doi: 10.1002/hup.1259 PMID: 22213434.
100. Hashizume H, Horibe T, Ohshima A, Ito T, Yagi H, Takigawa M. Anxiety accelerates T-helper 2-tilted immune responses in patients with atopic dermatitis. Br J Dermatol. 2005; 152(6):1161–4. Epub 2005/06/14. doi: 10.1111/j.1365-2133.2005.06449.x PMID: 15948976.

101. Romeo J, Wamberg J, Nova E, Diaz LE, Gomez-Martinez S, Marcos A. Moderate alcohol consumption and the immune system: a review. Br J Nutr. 2007; 98 Suppl 1:S111–5. Epub 2007/11/21. doi: 10.1017/S0007114507838049 PMID: 17922947.

102. Beulens JW, Rimm EB, Ascherio A, Spiegelman D, Hendriks HF, Mukamal KJ. Alcohol consumption and risk for coronary heart disease among men with hypertension. Ann Intern Med. 2007; 146(1):10–9. Epub 2007/01/04. PMID: 17200217.

103. Kaalberg H, Jacobsen S, Bengtsson C, Pedersen M, Padyukov L, Garred P, et al. Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies. Ann Rheum Dis. 2009; 68(2):222–7. Epub 2008/06/07. doi: 10.1136/ard.2007.086314 PMID: 18535114; PubMed Central PMCID: PMC2937278.

104. Room R, Babor T, Rehm J. Alcohol and public health. Lancet. 2005; 365(9458):519–30. Epub 2005/02/12. doi: 10.1016/S0140-6736(05)17870-2 PMID: 15705462.

105. Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. Psychol Rev. 2001; 108(1):4–32. Epub 2001/02/24. PMID: 11212632.

106. Rietveld S, Karsdorp PA, Mulder BJ. Heartbeat sensitivity in adults with congenital heart disease. Int J Behav Med. 2004; 11(4):203–11. Epub 2005/01/20. doi: 10.1207/s15327558ijbm1104_3 PMID: 15657020.

107. Domshke K, Stevens S, Pflieger B, Gerlach AL. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin Psychol Rev. 2010; 30(1):1–11. Epub 2009/09/16. doi: 10.1016/j.cpr.2009.08.008 PMID: 19751958.

108. Holoainen IE. Seizures in the developing brain: cellular and molecular mechanisms of neuronal damage, neurogenesis and cellular reorganization. Neurochem Int. 2008; 52(6):935–47. Epub 2007/12/21. doi: 10.1016/j.neuint.2007.10.021 PMID: 18093696.

109. Uher R, Treasure J. Brain lesions and eating disorders. J Neurol Neurosurg Psychiatry. 2005; 76(6):852–7. Epub 2005/05/18. doi: 10.1136/jnnp.2004.048819 PMID: 15897510; PubMed Central PMCID: PMC1739667.

110. Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, et al. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature. 1995; 374(6522):542–6. Epub 1995/04/06. doi: 10.1038/374542a0 PMID: 7700379.

111. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the US National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62(6):593–602. doi: 10.1001/archpsyc.62.6.593 PMID: 15939837.

112. Simon GE, Von Korff M. Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. Epidemiol Rev. 1995; 17(1):221–7. PMID: 8521941.

113. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 2003; 60(8):837–44. doi: 10.1001/archpsyc.60.8.837 PMID: 12912767.

114. Lewinsohn PM, Striegel-Moore RH, Seeley JR. Epidemiology and natural course of eating disorders in young women from adolescence to young adulthood. J Am Acad Child Adolesc Psychiatry. 2000; 39(10):1284–92. doi: 10.1097/00004583-200010000-00016 PMID: 11026183.

115. Merikangas KR, Nakamura EF, Kessler RC. Epidemiology of mental disorders in children and adolescents. Dialogues Clin Neurosci. 2009; 11(1):7–20. PMID: 19432384; PubMed Central PMCID: PMC2807642.
119. Anandan C, Numatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy. 2010; 65(2):152–67. doi: 10.1111/j.1398-9995.2009.02244.x PMID: 19912154.

120. Duncan GE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999–2002. Arch Pediatr Adolesc Med. 2006; 160 (5):523–8. doi: 10.1001/archpedi.160.5.523 PMID: 16651496.

121. Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe—a systematic review. Eur J Neurol. 2005; 12(4):245–53. doi: 10.1111/j.1468-1331.2004.00992.x PMID: 15804240.

122. Mortz CG, Lauritsen JM, Bindseil-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. Br J Dermatol. 2001; 144(3):523–32. PMID: 11260009.

123. Newacheck PW, Taylor WR. Childhood chronic illness: prevalence, severity, and impact. Am J Public Health. 1992; 82(3):364–71. Epub 1992/03/01. PMID: 1536351; PubMed Central PMCID: PMC1694379.

124. Costello EJ, Erkanli A, Federman E, Angold A. Development of psychiatric comorbidity with substance abuse in adolescents: effects of timing and sex. J Child Psychol. 1999; 28(3):298–311. doi: 10.1002(S15374424jcpc280302 PMID: 10446679.

125. Hudson JI, Hiripi E, Pope HG Jr., Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007; 61(3):348–58. doi: 10.1016/j.biopsych.2006.03.040 PMID: 15374424 jcpc280302 PMID: 15804240.

126. Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. Arch Gen Psychiatry. 1997; 54(4):337–43. Epub 1997/04/01. PMID: 9107150.

127. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965; 58:295–300. Epub 1965/05/01. PMID: 14282879; PubMed Central PMCID: PMC1889526.

128. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012; 380(9836):37–43. Epub 2012/05/15. doi: 10.1016/S0140-6736(12)60249-2 PMID: 22579043.

129. Guthrie B, Saultz JW, Freeman GK, Haggerty JL. Continuity of care matters. Bmj. 2008; 337:a867. Epub 2008/08/09. doi: 10.1136/bmj.a867 PMID: 18687724.

130. Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am J Cardiol. 2011; 107 (7):972–9. Epub 2011/01/25. doi: 10.1016/j.amjcard.2010.11.017 PMID: 21256471.

131. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005; 4 (3):130–6. doi: 10.1016/j.autrev.2004.09.002 PMID: 15823498.
141. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. N Engl J Med. 2012; 366(4):321–9. doi: 10.1056/NEJMoa1012848 PMID: 22276822; PubMed Central PMCID: PMCPMC3336876.

142. Hillier TA, Pedula KL. Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. Diabetes Care. 2001; 24(9):1522–7. PMID: 11522693.

143. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005; 294(6):716–24. Epub 2005/08/11. doi: 10.1001/jama.294.6.716 PMID: 16091574.