Association of Depression and Anxiety With the Accumulation of Chronic Conditions

William V. Bobo, MD, MPH; Brandon R. Grossardt, MS; Sanya Virani, MD, MPH; Jennifer L. St Sauver, PhD, MPH; Cynthia M. Boyd, MD, MPH; Walter A. Rocca, MD, MPH

Abstract

IMPORTANCE Longitudinal associations between comorbid depression and anxiety with the accumulation of chronic illnesses are unclear, and questions remain about the contributions associated with each condition in the increasing prevalence of multimorbidity.

OBJECTIVE To compare the risk and rate of accumulating chronic conditions in people with depression, anxiety, and comorbid depression and anxiety vs individuals with neither depression nor anxiety.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used the Rochester Epidemiology Project medical records-linkage system to identify residents of Olmsted County, Minnesota, from January 1, 2005, to December 31, 2014, with follow-up ending December 31, 2017. The sample was divided into cohorts anchored at birthday ages of 20, 40, and 60 years. Individuals were classified at anchoring birthday age as having depression alone, anxiety alone, comorbid depression and anxiety, or neither depression nor anxiety (reference group), using electronically extracted diagnosis codes from the International Classification of Diseases, Ninth Revision (ICD-9) in the 5 years before each anchoring birthday. Data were analyzed from August 2020 through November 2021.

EXPOSURES Depression alone, anxiety alone, comorbid depression and anxiety, or neither depression nor anxiety (reference group).

MAIN OUTCOMES AND MEASURES The main outcome was sex-specific risk, calculated as hazard ratios (HRs) and rates of accumulation, calculated as mean annual incidence rates per 100 person-years, of 15 common chronic conditions within each birthday age cohort through the end of study.

RESULTS Among the 40360 individuals included across all 3 age cohorts, 21516 (53.3%) were women. After balancing cohorts on race, Hispanic ethnicity, education level, body mass index, smoking status, and calendar year at index birthday, the risk of accumulating chronic conditions was significantly increased among women with depression alone (cohort aged 20 years: HR, 1.20 [95% CI, 1.02-1.42]; cohort aged 40 years: HR, 1.20 [95% CI, 1.10-1.31]; cohort aged 60 years: HR, 1.09 [95% CI, 1.02-1.16]) and women with comorbid depression and anxiety (cohort aged 20 years: HR, 1.60 [95% CI, 1.28-1.99]; cohort aged 40 years: HR, 1.41 [95% CI, 1.21-1.65]; cohort aged 60 years: HR, 1.29 [95% CI, 1.15-1.44]) compared with referent women in the same birthday cohorts and in men with comorbid depression and anxiety compared with referent men in the cohort aged 20 years (HR, 1.77 [95% CI, 1.08-2.91]). For women, the rates of accumulation of conditions were significantly higher across birthday cohorts in the comorbid depression and anxiety group compared with the depression alone group (eg, cohort aged 20 years: difference, 1.2 [95% CI, 0.2-2.1] per 100 person-years) and reference group (eg, cohort aged 20 years: difference, 1.7 [95% CI, 0.9-2.6] per 100 person-years). For men, compared with the reference group, the rates of accumulation of conditions were significantly higher in men with comorbid depression and anxiety in the cohort aged 20 years (continued)
Abstract (continued)
(difference, 1.4 [95% CI, 0.1-2.6] per 100 person-years) and in men with depression in the cohort aged 40 years (difference, 2.0 [95% CI, 0.8-3.2] per 100 person-years).

CONCLUSIONS AND RELEVANCE In this cohort study, the risk of accumulating chronic conditions was increased with depression and comorbid depression and anxiety in women across the age span and in younger men with comorbid depression and anxiety. Compared with women without depression or anxiety, there was a more rapid rate of accumulation of chronic conditions in women with depression and anxiety individually and an even higher rate when depression and anxiety cooccurred.


Introduction
Depression and anxiety are associated with an increased risk of multimorbidity and premature death from natural causes, and may be associated with a more rapid accumulation of chronic medical conditions commonly observed in older people, a proxy for accelerated aging. Although a direct link between depression, anxiety, and accelerated aging has not been demonstrated, there is increasing evidence of shared biological mechanisms between depression and chronic conditions known to occur later in life, as well as measures of cellular aging.

Depression and anxiety disorders frequently cooccur, which is associated with greater illness severity and worse treatment outcomes than with either condition alone. Depression and anxiety are also associated with increased risk of comorbid general medical illnesses, suggesting that comorbid depression and anxiety may further increase the risk of multimorbidity from chronic illnesses beyond the risks associated with each individually. Previous longitudinal research has focused mainly on the associations between baseline depression or anxiety and the later occurrence of single chronic general medical conditions. Studies focused on depression or anxiety and the risk of multiple illnesses have been cross-sectional in nature or have considered longitudinal associations with individual conditions among those illnesses and not the risks or rates of acquiring cooccurring illnesses. Very few studies have directly compared the longitudinal risks of new chronic conditions or cooccurring conditions in people with depression, anxiety, and comorbid depression and anxiety within a single cohort, and to our knowledge, none has compared the rates of accumulation of chronic illnesses among these same groups of individuals. This is an important question, given the relatively early ages of onset of depression and anxiety and the possibility of a synergistic interaction of depression and anxiety in increasing the prevalence and costs of multimorbidity worldwide.

Thus, we conducted a population-based retrospective cohort study to examine the associations of diagnosed depression, anxiety, and comorbid depression and anxiety with the accumulation of 15 common chronic conditions in 3 birthday age cohorts. We hypothesized that in all 3 cohorts the risks and rates of accumulation would be higher in cohorts with depression, anxiety, and comorbid depression and anxiety than in a reference cohort with neither depression nor anxiety and that the risk and rate of accumulation would be highest in individuals with comorbid depression and anxiety. We investigated these associations separately for women and men because of known sex differences in the occurrences of depression, anxiety, and several chronic conditions and explored patterns of all-cause mortality for the main exposure groups within each birthday cohort.
Methods

The Mayo Clinic and Olmsted Medical Center institutional review boards approved all research activities in this cohort study and waived informed consent, per Minnesota state privacy law, Statute §144.335. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Data Source and Study Population

For this retrospective cohort study, the Rochester Epidemiology Project (REP) medical records-linkage system was used to identify residents of Olmsted County, Minnesota, in the 10-year period between January 1, 2005, and December 31, 2014. We excluded individuals who did not reach at least 1 anchoring birthday during the study period (<5%), and individuals who did not have any medical record with research authorization, per Minnesota legal requirements (<5%). The population enumeration obtained using the REP is similar to that obtained by the US Census, indicating that nearly the entire population of Olmsted County is captured by the system. Details about the REP have been previously reported.48,49

The sample was divided into cohorts anchored at birthday ages of 20, 40, and 60 years. The cohort aged 20 years included all individuals who celebrated their 20th birthday as Olmsted County residents between January 1, 2005, and December 31, 2014, and they were followed-up from the date of their 20th birthday (index date) through the end of the study, defined as the earliest of 3 dates: the date of death, the date of last medical contact with the REP, or December 31, 2017 (to allow for at least 3 years of follow-up after each of the anchoring birthdays). The cohorts aged 40 and 60 years were similarly defined, except that index dates occurred on the 40th or 60th birthday.

Individuals were excluded from our study if on the index birthday date they had evidence of diagnosed primary psychotic disorders (International Classification of Diseases, Ninth Revision [ICD-9] codes 295.10, 297.x, 298.3, 298.4, 298.8, or 298.9), bipolar disorders (ICD-9 codes 296.0x, 296.1, 296.4x, 296.5x, 296.6x, 296.7, or 296.8x), eating disorders (ICD-9 codes 307.1 or 307.5x), dementia or delirium (ICD-9 codes 290x, 293.0, 293.1, 294x, 310.0, 310.1, 310.8x, 310.9, 331.0, 331.1x, 331.2, 331.7, 331.82, or 797), autism (ICD-9 codes 299.00 or 299.01), or alcohol or other substance use disorders (ICD-9 codes 291, 292, 303x, 304, 305x, or V113) based on the presence of at least 2 corresponding ICD-9 diagnosis codes separated by more than 30 days in the 5 years before the index date (eFigure 1 in the Supplement). These conditions were excluded because of their associations with multimorbidity and mortality risk and because their presence may complicate the determination of depression and anxiety as exposures.51-56

Main Exposure Groups

Main exposure groups in each age cohort were depression, anxiety, and comorbid depression and anxiety. Depression and anxiety were defined using ICD-9 diagnostic codes50 for a unipolar depressive disorder or an anxiety disorder (eTable 1 in the Supplement). All index date birthdates were before the transition to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)57 codes for clinical practice on October 1, 2015; therefore, only ICD-9 codes50 were used to define depression and anxiety. Persons met criteria for depression or anxiety if they received 2 or more diagnostic codes for the condition separated by more than 30 days in the 5 years before the index date. Individuals with depression alone met the definition for depression (but not anxiety), and individuals with anxiety alone met the definition for anxiety (but not depression). Individuals with comorbid depression and anxiety met the definitions for both depression and anxiety. Reference groups in each birthday age cohort included individuals who did not meet the definition for either depression or anxiety in the 5 years before the index date.
Accumulation of Chronic Conditions

The primary outcome for this study was the accumulation of newly diagnosed chronic conditions. We considered 15 of 20 chronic conditions recommended by the US Department of Health and Human Services (eTable 2 in the Supplement). The modified list of chronic conditions excluded depression, schizophrenia, substance use disorders, dementia or delirium, and autism, given our focus on studying the associations of depression and anxiety with the accumulation of chronic conditions and because depression defined 2 of the exposure groups in this study. Chronic conditions were defined based on having 2 or more ICD-9 or ICD-10 diagnosis codes for a given condition separated by more than 30 days. This definition has been shown to result in a higher positive predictive value for identifying chronic conditions than relying on a single diagnosis code and is thus preferable for cohort studies. The date of onset of a given condition was defined as the date of the earliest diagnosis code that occurred more than 30 days after the first corresponding diagnosis code. According to this approach, acute events (eg, stroke) leading to death were analytically censored at the time of proximate death, consistent with this study’s focus on the accumulation of chronic conditions. Both ICD-9 and ICD-10 diagnosis codes were used to assess chronic conditions during follow-up (extending after October 1, 2015).

All-Cause Mortality

All-cause mortality was an exploratory outcome in this study. Mortality was assessed by extracting REP electronic files, which contain detailed mortality information for residents of Olmsted County, including dates of death and causes of death as recorded on death certificates using ICD-9 and ICD-10 diagnosis codes.

Covariates

Age at cohort entry was fixed by design to index birthdays at ages 20, 40, and 60 years. Information on sex, self-reported race and ethnic group (Hispanic, non-Hispanic) as defined by the US Census Bureau, and self-reported education level were electronically extracted from REP indices for all cohort members. Race and ethnicity were included as covariates given the associations of both factors with the level of burden from chronic diseases and relative rates of chronic disease accumulation. Information on body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and smoking status at index date was electronically extracted from medical records.

Statistical Analysis

For each age cohort, the mean number of chronic conditions over time (years after the index birthday) was plotted by exposure group in men and women separately using Aalen-Johansen curves. To compare the risks of accumulating chronic conditions, hazard ratios (HRs) were estimated using Anderson-Gill regression models. Each event was treated equally; therefore, the analyses focused on time to the first event, then to the second event, and so forth. Adjusted HRs were calculated using inverse probability weights (IPWs) derived from generalized boosting models that included indicators for categories of covariates on which to balance for potential confounders. The covariates included for constructing balancing weights were race (in categories as Asian, Black, White, or other or unknown, including individuals who identified as Native American or Alaskan Native, who specifically indicated mixed race, or for whom no race information was available from any of their medical records), ethnicity (Hispanic or non-Hispanic), level of education (in categories as high school or less, some college, ≥4 years of college, and unknown), BMI (in categories as <25, 25 to <30, ≥30, and unknown), smoking status (never smoker, former smoker, current smoker, and unknown), and calendar year at index date (as an integer from 2005 through 2014).

The 15 chronic conditions were not excluded at index birthdays. Instead, all exposure groups within each birthday age cohort were balanced at index birthday on the listed covariates and on the prevalence of the 15 chronic conditions using IPWs. Using this approach, the Anderson-Gill regression...
models included only newly diagnosed (ie, incident) chronic conditions as outcomes. The balance across exposure groups obtained with IPWs was examined using the absolute value of the standardized difference of means, and a standardized difference of means less than 0.25 was defined as good balance of covariates. For sex-stratified analyses, IPWs were normalized so that the sum of the weights within a sex stratum equaled the number of individuals originally in that stratum. We tested for additive and multiplicative interactions between depression and anxiety with the risk of accumulating chronic conditions under the null hypothesis that no excess risk existed due to the interaction.

To compare rates of accumulating new chronic conditions, we calculated the sex-specific mean annual incidence rate of accumulation of new chronic conditions per 100 person-years by exposure group and separately for each age cohort. The rates (and corresponding 95% CIs) were calculated by dividing the total number of newly acquired chronic conditions by the total number of person-years of follow-up in each cohort (and multiplying by 100). Excess accumulation of chronic conditions was calculated by subtracting pairwise incidence rates and constructing 95% CIs for the differences (eg, rates of accumulating new chronic conditions in individuals with comorbid depression and anxiety vs referent individuals).

For exploratory analyses, Kaplan-Meier survival curves were constructed with death from any cause as the outcome. Unweighted HRs and weighted HRs (with weights calculated as previously described) were calculated using Cox proportional hazard models. The proportionality assumption was tested visually and by including a time-dependent coefficient in the Cox models.

Analyses for the risks (HRs) of accumulation of chronic conditions were designed to assess relative differences between exposure groups. Analyses for the rates (incidence) of accumulation of chronic conditions were designed to assess absolute differences between exposure groups. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute) and using R statistical software version 3.6.2 (R Project for Statistical Computing). All statistical tests of significance were undertaken at the conventional 2-tailed level of \( \alpha = .05 \).

**Results**

**Demographic and Clinical Characteristics**

Among 40,360 individuals included across all 3 age cohorts, 21,516 (53.3%) were women. According to self-report, 1830 individuals (4.5%) were Asian, 1696 individuals (4.2%) were Black, and 34,840 individuals (86.3%) were White. The study cohorts included 14,810 people in the cohort aged 20 years, 13,060 people in the cohort aged 40 years, and 12,490 people in the cohort aged 60 years (eFigure 1 in the Supplement). In the cohort aged 20 years, 1346 individuals (9.1%) had depression alone, 474 individuals (3.2%) had anxiety alone, and 512 individuals (3.5%) had comorbid depression and anxiety on the index date. Similar frequencies of depression, anxiety, and comorbid depression-anxiety were observed in the cohorts aged 40 or 60 years (Table 1). Exposure groups were not highly imbalanced before IPW (eFigures 2 in the Supplement); however, the use of IPW improved the balance of baseline characteristics across exposure groups, particularly for the comorbid depression and anxiety exposure group (standardized differences of means for nearly all variables were <0.25).

**Multimorbidity Accumulation in Women**

Estimates for risk of accumulating chronic conditions in each birthday age cohort are summarized in Table 2 and comparative rates of multimorbidity accumulation are summarized in Table 3. In both unweighted and weighted models and in all 3 cohorts, the risk of accumulating chronic conditions was significantly increased in women with depression (cohort aged 20 years: weighted HR, 1.20 [95% CI, 1.02-1.42]; cohort aged 40 years: weighted HR, 1.20 [95% CI, 1.10-1.31]; cohort aged 60 years: weighted HR, 1.09 [95% CI, 1.02-1.16]) and women with comorbid depression and anxiety (cohort aged 20 years: weighted HR, 1.60 [95% CI, 1.28-1.99]; cohort aged 40 years: weighted HR, 1.41 [95% CI, 1.21-1.65]; cohort aged 60 years: weighted HR, 1.29 [95% CI, 1.15-1.44]) compared with
Table 1. Sociodemographic and Clinical Characteristics of Individuals With Depressive Disorders and/or Anxiety Disorders, Separately Within 3 Age Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Birthday cohort, No. (%)</th>
<th>Age 20 y (n = 14 810)</th>
<th>Age 40 y (n = 13 060)</th>
<th>Age 60 y (n = 12 490)</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Women</td>
<td>6 211 (49.8)</td>
<td>8 663 (64.9)</td>
<td>3 717 (27.5)</td>
<td>5 356 (51.0)</td>
</tr>
<tr>
<td>Men</td>
<td>6 267 (50.2)</td>
<td>4 909 (35.1)</td>
<td>9 343 (72.5)</td>
<td>5 139 (49.0)</td>
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<tr>
<td><strong>Follow-up, median (IQR), y</strong></td>
<td>5.9 (3.8-8.7)</td>
<td>6.5 (4.2-9.2)</td>
<td>5.3 (3.7-7.7)</td>
<td>4.7 (3.9-8.4)</td>
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<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
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<tr>
<td>Asian</td>
<td>573 (4.6)</td>
<td>29 (2.2)</td>
<td>15 (3.2)</td>
<td>15 (2.9)</td>
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<td>Black</td>
<td>833 (6.7)</td>
<td>45 (3.3)</td>
<td>13 (2.7)</td>
<td>19 (3.7)</td>
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<tr>
<td>White</td>
<td>10 341 (82.9)</td>
<td>1 185 (88.0)</td>
<td>419 (88.4)</td>
<td>320 (87.5)</td>
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<tr>
<td>Other or unknown*</td>
<td>731 (5.9)</td>
<td>87 (6.5)</td>
<td>27 (5.7)</td>
<td>30 (5.9)</td>
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<tr>
<td>Hispanic</td>
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<td>78 (5.8)</td>
<td>26 (5.5)</td>
<td>81 (5.6)</td>
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<tr>
<td>Non-Hispanic</td>
<td>11 846 (94.9)</td>
<td>1 185 (88.0)</td>
<td>419 (88.4)</td>
<td>320 (87.5)</td>
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<tr>
<td><strong>Education level</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>≤High school</td>
<td>2 390 (19.2)</td>
<td>337 (25.0)</td>
<td>100 (21.1)</td>
<td>121 (23.6)</td>
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<tr>
<td>Some college</td>
<td>3 578 (28.7)</td>
<td>482 (35.6)</td>
<td>158 (32.5)</td>
<td>193 (38.7)</td>
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<tr>
<td>≥4 y college</td>
<td>3 071 (23.8)</td>
<td>258 (19.3)</td>
<td>105 (21.1)</td>
<td>121 (23.6)</td>
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<tr>
<td>Unknown</td>
<td>3 439 (26.2)</td>
<td>269 (20.0)</td>
<td>93 (19.6)</td>
<td>85 (16.6)</td>
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<tr>
<td><strong>BMI</strong></td>
<td></td>
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<tr>
<td>&lt;25</td>
<td>8 653 (63.3)</td>
<td>874 (64.9)</td>
<td>339 (71.5)</td>
<td>333 (61.1)</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>8 653 (63.3)</td>
<td>874 (64.9)</td>
<td>339 (71.5)</td>
<td>333 (61.1)</td>
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<tr>
<td>≥30</td>
<td>8 653 (63.3)</td>
<td>874 (64.9)</td>
<td>339 (71.5)</td>
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<td>Unknown</td>
<td>8 653 (63.3)</td>
<td>874 (64.9)</td>
<td>339 (71.5)</td>
<td>333 (61.1)</td>
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<td><strong>Smoking status</strong></td>
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<tr>
<td>Never</td>
<td>6 243 (50.1)</td>
<td>523 (38.9)</td>
<td>250 (52.7)</td>
<td>407 (38.9)</td>
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<tr>
<td>Former</td>
<td>631 (51.3)</td>
<td>152 (11.3)</td>
<td>41 (8.6)</td>
<td>137 (26.8)</td>
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<tr>
<td>Current</td>
<td>988 (79.7)</td>
<td>267 (19.8)</td>
<td>47 (9.9)</td>
<td>137 (26.8)</td>
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<td><strong>Other conditions</strong></td>
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<tr>
<td>Hypertension</td>
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<td>5 (0.4)</td>
<td>4 (0.8)</td>
<td>10 (0.4)</td>
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<td>CHF</td>
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<td>5 (0.4)</td>
<td>4 (0.8)</td>
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<tr>
<td>CAD</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
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<tr>
<td>Carotid artery stenosis</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
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<tr>
<td>Previous stroke</td>
<td>6 (0.5)</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
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<td>In a relationship</td>
<td>1203 (9.6)</td>
<td>144 (10.7)</td>
<td>50 (1.5)</td>
<td>40 (0.8)</td>
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<tr>
<td>Divorced</td>
<td>529 (5.0)</td>
<td>54 (4.0)</td>
<td>9 (1.7)</td>
<td>17 (1.4)</td>
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</table>

*Continued...*
Table 1. Sociodemographic and Clinical Characteristics of Individuals With Depressive Disorders and/or Anxiety Disorders, Separately Within 3 Age Cohorts (*continued*)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Birthday cohort, No. (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age 20 y (n = 14 810)</td>
<td>Age 40 y (n = 13 060)</td>
<td>Age 60 y (n = 12 490)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Referent (n = 12 478)</td>
<td>Referent (n = 10 495)</td>
<td>Referent (n = 10 429)</td>
<td></td>
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<tr>
<td>Depression alone</td>
<td>Depression alone (n = 1346)</td>
<td>Depression alone (n = 1443)</td>
<td>Depression alone (n = 1328)</td>
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<tr>
<td>Anxiety alone</td>
<td>Anxiety alone (n = 474)</td>
<td>Anxiety alone (n = 600)</td>
<td>Anxiety alone (n = 334)</td>
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<tr>
<td>DA</td>
<td>DA (n = 512)</td>
<td>DA (n = 522)</td>
<td>DA (n = 529)</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cancer</th>
<th>CKD</th>
<th>COPD</th>
<th>Diabetes</th>
<th>Hepatitis</th>
<th>HIV Infection</th>
<th>Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent (n = 12 478)</td>
<td>46 (0.4)</td>
<td>35 (0.3)</td>
<td>113 (0.9)</td>
<td>89 (0.7)</td>
<td>24 (0.2)</td>
<td>2 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td>Age 40 y (n = 10 495)</td>
<td>222 (2.1)</td>
<td>97 (0.9)</td>
<td>149 (1.4)</td>
<td>512 (4.9)</td>
<td>76 (0.7)</td>
<td>8 (0.1)</td>
<td>28 (0.3)</td>
</tr>
<tr>
<td>Age 60 y (n = 10 429)</td>
<td>819 (7.9)</td>
<td>246 (2.4)</td>
<td>312 (3.0)</td>
<td>2252 (21.6)</td>
<td>68 (0.7)</td>
<td>3 (&lt;0.1)</td>
<td>308 (3.0)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DA, comorbid depression and anxiety.

* Individuals were excluded at index birthday if they had autism, dementia or delirium, schizophrenia or psychoses, or substance abuse disorders. In addition, individuals with a depressive disorder in the context of a bipolar disorder and individuals with an eating disorder were excluded at index date.

b Includes individuals who identified as Native American or Alaskan Native, who specifically indicated mixed race, or for whom no race information was available from any of their medical records.

c Cancer includes all types of cancer except nonmelanoma skin cancer.
women with neither depression nor anxiety. For women in the cohort aged 40 years, anxiety was also associated with higher risk compared with referent women (weighted HR, 1.24; 95% CI, 1.08-1.43) (Table 2; Figure 1).

For women, the rates of accumulation of chronic conditions were significantly higher in all 3 birthday cohorts for the comorbid depression and anxiety group than the depression group and reference group and higher than the anxiety group for the cohort aged 60 years (Table 3; Figure 2). The differences in rates of accumulation of chronic conditions were significantly higher for women with depression than women in the reference group in all 3 birthday cohorts (cohort aged 20 years):

<table>
<thead>
<tr>
<th>Table 2. Accumulation of Chronic Conditions Stratified by Age Cohort and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birthday cohort</strong></td>
</tr>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td><strong>Age 20 y</strong></td>
</tr>
<tr>
<td>Referent</td>
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<td>Depression alone</td>
</tr>
<tr>
<td>Anxiety alone</td>
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<tr>
<td>Comorbid depression and anxiety</td>
</tr>
<tr>
<td><strong>Age 40 y</strong></td>
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<tr>
<td>Referent</td>
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<tr>
<td>Depression alone</td>
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<tr>
<td>Anxiety alone</td>
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<tr>
<td>Comorbid depression and anxiety</td>
</tr>
<tr>
<td><strong>Age 60 y</strong></td>
</tr>
<tr>
<td>Referent</td>
</tr>
<tr>
<td>Depression alone</td>
</tr>
<tr>
<td>Anxiety alone</td>
</tr>
<tr>
<td>Comorbid depression and anxiety</td>
</tr>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td><strong>Age 20 y</strong></td>
</tr>
<tr>
<td>Referent</td>
</tr>
<tr>
<td>Depression alone</td>
</tr>
<tr>
<td>Anxiety alone</td>
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<tr>
<td>Comorbid depression and anxiety</td>
</tr>
<tr>
<td><strong>Age 40 y</strong></td>
</tr>
<tr>
<td>Referent</td>
</tr>
<tr>
<td>Depression disorder alone</td>
</tr>
<tr>
<td>Anxiety alone</td>
</tr>
<tr>
<td>Comorbid depression and anxiety</td>
</tr>
<tr>
<td><strong>Age 60 y</strong></td>
</tr>
<tr>
<td>Referent</td>
</tr>
<tr>
<td>Depression alone</td>
</tr>
<tr>
<td>Anxiety alone</td>
</tr>
<tr>
<td>Comorbid depression and anxiety</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; M, multiplicative.

* Adjusted models are weighted using weights developed from generalized boosting models to balance the 4 exposure groups at index birthday on potential confounders, including calendar year of birthday, race, ethnicity, education, smoking status, body mass index, and prevalence of each of the 15 chronic conditions.

** Events for accumulation of additional chronic conditions included 15 chronic conditions: hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, hepatitis, HIV infection, and osteoporosis.

† Time-to-event HRs are estimated from Andersen-Gill models.

* The M interaction test is given by including the term (depression × anxiety) in the regression model.

* The additive interaction test P value is calculated from the relative excess risk due to interaction method.65

Formal tests of sex-interaction were performed for adjusted analyses to determine whether the profile of HRs in women differed from those in men. The global test of sex-interaction simultaneously tests whether the HRs for depression alone, anxiety alone, and comorbid depression and anxiety differed between men and women. The global sex-interaction test was not statistically significant for the age 20 years cohorts (P = .78); however, the global sex-interaction test was statistically significant in the age 40 years (P = .02) and age 60 years (P = .008) cohorts.
0.6 [95% CI, 0.1-1.1] per 100 person-years; cohort aged 40 years: 1.7 [95% CI, 0.9-2.4] per 100 person-years; cohort aged 60 years: 1.7 [95% CI, 0.6-2.8] per 100 person-years), and for women with anxiety compared with the reference group in only the cohort aged 40 years (2.1 [95% CI, 0.9-3.3] per 100 person-years) (Figure 2). Women with comorbid depression and anxiety accumulated from 1.7 (95% CI, 0.9-2.6) more comorbid conditions per 100 person-years in the cohort aged 20 years to 5.7 (95% CI, 3.7-7.6) more comorbid conditions per 100 person-years in the cohort aged 60 years than women in the reference groups. Women with comorbid depression and anxiety accumulated more chronic conditions per 100 person-years than women with depression alone in all age cohorts and more than women with anxiety alone only in the cohort aged 60 years (Figure 2).

**Multimorbidity Accumulation in Men**

For men, there was a significantly higher risk for accumulating chronic conditions with depression and comorbid depression and anxiety compared with men in the reference group in the cohort aged 20 years in unweighted models; however, the increased risk remained significant only for comorbid depression and anxiety in weighted models (HR, 1.77 [95% CI, 1.08-2.91]) (Table 2; Figure 1). The risk of accumulating chronic conditions was also significantly increased with comorbid depression and anxiety compared with men in the reference group in the cohort aged 40 years, but only in unweighted models (Table 2).

Rates of accumulation of chronic conditions were highest for men with comorbid depression and anxiety in all birthday cohorts (Table 3). However, compared with men in the reference group, the differences in rates of accumulation of chronic conditions were significantly higher in men with comorbid depression and anxiety only in the cohort aged 20 years (difference, 1.4 [95% CI, 0.1-2.6] per 100 person-years) and for men with depression in only the cohort aged 40 years (difference, 2.0 [95% CI, 0.8-3.2] per 100 person-years) (Table 3; Figure 2).

**Statistical Tests for Interaction**

Formal statistical tests for interaction were conducted to analyze the joint associations of depression and anxiety with the risk of accumulating chronic conditions. For women and men, statistical tests for additive or multiplicative interaction between depression and anxiety on the risk of accumulating chronic conditions were not statistically significant (Table 2).

**Exploratory Analyses: Mortality**

The results of exploratory analyses of all-cause mortality risk are summarized in eTable 3 in the Supplement and are visually displayed in eFigure 3 in the Supplement for the cohorts aged 60 years only. For women, depression and comorbid depression and anxiety were significantly associated with all-cause mortality in the cohorts aged 40 and 60 years in unweighted models, but only depression was associated with all-cause mortality in both birthday cohorts in weighted models.

### Table 3. Mean Annual Rate of Accumulation of New Conditions Stratified by Age Cohort and Sex

<table>
<thead>
<tr>
<th>Birthday cohort</th>
<th>Group, rate of new chronic conditions per 100 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Age 20 y</td>
<td>2.84 (2.68-3.00)</td>
</tr>
<tr>
<td>Age 40 y</td>
<td>8.49 (8.22-8.76)</td>
</tr>
<tr>
<td>Age 60 y</td>
<td>19.7 (19.3-20.1)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Age 20 y</td>
<td>1.89 (1.76-2.03)</td>
</tr>
<tr>
<td>Age 40 y</td>
<td>9.69 (9.39-9.99)</td>
</tr>
<tr>
<td>Age 60 y</td>
<td>22.8 (22.4-23.3)</td>
</tr>
</tbody>
</table>
Figure 1. Accumulation of Chronic Conditions Over Time in Women and Men With Depression, Anxiety, Comorbid Depression and Anxiety, and Neither Depression nor Anxiety (Referent Group)

A. Age 20 y

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Depression only</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Anxiety only</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>0.6</td>
<td>0.6</td>
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</table>

B. Age 40 y

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Depression only</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Anxiety only</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

C. Age 60 y

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Depression only</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Anxiety only</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>4.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>
(eTable 3 in the Supplement). There was no significant association between anxiety and mortality for women in any of the cohorts.

For men, the risk of mortality was significantly increased in unweighted and weighted models for depression, but not comorbid depression and anxiety or anxiety alone, in the cohort aged 60 years (eTable 3 in the Supplement). The risk of mortality was not significantly increased for men in any exposure group in the cohorts aged 20 or 40 years.

Discussion

To our knowledge, this cohort study is the first study comparing the longitudinal risk of accumulating chronic conditions in individuals with depression, anxiety, or comorbid depression and anxiety across the age spectrum within a geographically defined population. The risk of accumulating chronic conditions was significantly higher in women with depression and comorbid depression and anxiety than women in the reference group in each of 3 birthday cohorts (ages 20, 40, and 60 years), with similar observations for men in the cohort aged 20 years. Rates of accumulation of chronic conditions were also highest for women and men with comorbid depression and anxiety.

An extensive body of prior research has documented longitudinal associations of depression, anxiety, or depressive and anxious symptoms with the later onset or diagnoses of individual cardiovascular diseases,19,24-28,30,66,67 metabolic diseases,19,21,22 certain types of cancer,20 atopic illnesses,23 and chronic or recurring pain syndromes.24,69 More recent work, mainly cross-sectional or retrospective in nature, has focused on the risk of multiple chronic conditions, showing more chronic health conditions in people with depression and individuals with anxiety.31-34,70 Longitudinal studies of mood or anxiety disorders and the later occurrence of multiple chronic conditions are far fewer, but they also reported associations of depression or anxiety with individual conditions,36-38 including one of the largest studies to date, a 2020 study by Momen et al,40 that showed associations of mood disorders (including unipolar and bipolar depressive disorders) and neurotic disorders (including anxiety disorders, posttraumatic stress disorder [PTSD] and related conditions, obsessive-compulsive disorder, and somatoform disorders) with increases in incident general medical conditions within 9 broad categories, each considered individually. In that study,40 the cumulative incidence of each of the 9 groups of conditions was significantly higher in people with
mood disorders and in people with neurotic disorders; however, comorbid depression and anxiety as
an exposure group and the cumulative incidence of multiple conditions were not included. There are
few studies of the cumulative burden of incident chronic illnesses in people with baseline depression
or anxiety. The English Longitudinal Study of Ageing71 showed a higher incidence of general medical
conditions and higher illness burden (based on the number of incident conditions) in people with
baseline depression. Another longitudinal study from Australia72 documented a greater than 4-fold
increase in the cumulative 20-year incidence of multiple chronic physical conditions in a cohort of
women with depressive symptoms compared with a matched cohort of women without depression.
Our results extend beyond prior research by documenting a more rapid rate of accumulation of newly
diagnosed chronic conditions among women over time with depression and anxiety separately, and
an even higher rate of accumulation when depression and anxiety cooccurred.

The identification of treatable risk factors for multimorbidity, such as depression and anxiety, is
vital from a public health perspective because of the high prevalence and associated costs of
multimorbidity,42,43 which are expected to continue to increase.73 Depression and anxiety are
associated with incident general medical illnesses at a scale similar to obesity and smoking.74 To our
knowledge, no previous studies have directly compared the longitudinal rates of accumulation of
chronic illnesses among people with depression, anxiety, and comorbid depression and anxiety. This
knowledge gap is important because approximately half of individuals with depression have a
comorbid anxiety disorder, and vice-versa.75,76 A cross-sectional study documented a higher lifetime
risk of various prevalent chronic conditions (mainly cardiovascular diseases and chronic pain) in
people with comorbid depression and anxiety compared with individuals with either condition
alone.41 Our study contributes longitudinal findings showing higher rates of accumulation of chronic
diseases with comorbid depression and anxiety compared with neither depression nor anxiety or
with depression alone across the age span in women and compared with neither depression nor
anxiety in younger men.

This study focused on the associations between depression and anxiety with the accumulation of
chronic conditions, a process that may be driven by age-related homeostatic dysregulation across
multiple organ systems.46,77 Our findings suggest that common mechanisms may underly depression
and anxiety as well as aging and that these mechanisms may be magnified when depression and
anxiety cooccur. Multiple biological mechanisms are implicated in this process, including chronic
inflammation, neuroendocrine dysregulation, oxidative stress, mitochondrial dysfunction, and
others.78-82 Nearly all of these mechanisms are associated with psychosocial stress,83 thus providing
an additional link between common stress-mediated psychiatric disorders, like depression and
anxiety, and chronic somatic illnesses. From a translational viewpoint, the relative overexpression of
specific biological mechanisms in individuals with depression or anxiety, activated or enhanced by
the cumulative effects of stress, may be reflected in specific multimorbidity patterns that involve
distinct groups of chronic somatic illnesses.

For women aged 40 or 60 years, the maximum pairwise differences in rates of accumulation of
new conditions between comorbid depression and anxiety and depression and anxiety separately
was 4.6 new conditions per 100 person-years. However, even this increase may be clinically
significant. Prior research has shown that multimorbidity is a known risk factor for mortality,6,84 and
the differences in accumulation of chronic conditions in our study may be large enough to contribute
to the higher risk of all-cause mortality with comorbid depression and anxiety. Moreover, just 1 newly
diagnosed chronic illness per 12 to 36 months is associated with increasing the risk of functional
dependency by 2-fold, a known factor involved in the association between multimorbidity and
mortality in older adults.85 Our findings support the need for managing comorbid depression and
anxiety,86 which may help lower the risk of premature mortality associated with multimorbidity.

A 2018 study87 reported that depressive or anxiety symptom severity, rather than discrete
diagnoses, is associated with multimorbidity development. Our focus on depression and anxiety
disorders was intentional, because we used diagnostic codes for discrete depressive and anxiety
disorders. Although depression with anxiety symptoms is a useful illness subtype,88,89 documented
associations between cooccurring depressive and anxiety disorders and worse health and functioning provide clinical justification for our approach.12-15

The anxiety disorders in this study included PTSD and acute stress disorder (ASD), consistent with the definition of anxiety disorders in the Medical Expenditure Panel Survey.90 There were at least 3 reasons for including PTSD and ASD as anxiety disorders in this study. First, PTSD and ASD have been classified as trauma- and stressor-related disorders, separate from anxiety disorders, only since 2013.91 Therefore, during nearly the entire time in which cohort members were identified (January 1, 2005, to December 31, 2014), ASD and PTSD were considered anxiety disorders. Second, although the broader emotional experience of patients with PTSD and ASD extends beyond fear and anxiety,92 both are central constructs for the development of PTSD and ASD, and fear and avoidance are fundamental targets of treatment for both conditions.93 And finally, PTSD has been associated with increased risk for a variety of chronic health problems, including incident cardiometabolic diseases, even after adjusting for depression.25,26,40

The association between sex and multimorbidity has received limited investigation.94,95 This work highlights potentially important sex differences in the association between depression and anxiety and multimorbidity accumulation. Our study design was based on known sex dimorphisms in the prevalence of depression, anxiety, and several chronic diseases44-46,96 and was consistent with recent calls for additional studies on sex differences in somatic-mental multimorbidity to support precision medicine.97,98 We did not have access to data on self-reported gender identity, so we were unable to examine associations involving gender, separate from biological sex, on patterns of multimorbidity acquisition.

We found an increased risk of accumulating chronic conditions with depression and comorbid depression-anxiety in women across all age groups, but only in younger men. Although differences related to reporting of conditions, socioeconomic roles, and other social factors cannot be excluded, the susceptibility to increased risk of accumulating chronic conditions in women across the age span in our study may reflect heightened risk for stress- and trauma-related disorders, chronicity of anxiety symptoms, and cumulative outcomes associated with increased stress and inflammation in women, compared with men.45,99,100 In particular, potential sex differences in the sensitivity to outcomes associated with chronically increased stress-system activation and inflammation in the body may translate to not only higher risk of depression and anxiety,101,102 but also disproportionately increased accumulation of a wide range of stress-related chronic illnesses, including (but not limited to) cardiovascular diseases, metabolic disorders, obesity, certain cancers, atopic diseases, and pain syndromes, in women.103-105

The associations of depression and comorbid depression and anxiety with increased risk of accumulating chronic conditions isolated to only some age cohorts in men is more difficult to explain. The increasing prevalence of internalizing problems (characterized by depression and anxiety) impacting 21st century youth have been reported to be more pronounced in adolescent girls than boys.106,107 Such differences may reflect higher detection rates of mood and anxiety disorders among girls, consistent with the broader literature pointing to higher rates of undiagnosed mood and anxiety disorders in men relative to women.108 Improved mental health literacy and better recognition of male-typical symptoms of depression and anxiety may have resulted in reduced barriers to seeking or receiving treatment for mental health conditions among the men in the cohort aged 20 years relative to those in older cohorts. Such a difference may have resulted in the occurrence of more pairings of depression and/or anxiety with chronic condition in the medical records of younger men than older men in our study, a hypothesis that we were not able to test with this study design.

Our study had a number of strengths, including access to medical record data for all conditions of interest and for the full spectrum of primary and specialty care within a geographically defined population. The study cohorts included all age, sex, and racial and ethnicity groups, regardless of socioeconomic status, insurance status, and health care delivery setting.49 All 15 chronic health conditions in this research were chosen by the US Department of Health and Human Services as
being high public health priorities for the nation and are among those suggested for international multimorbidity research. Additionally, the code sets used in this research were previously validated against medical record review of a representative sample of the underlying population.

Limitations
This study has some limitations. Mental health conditions and multimorbidity have a bidirectional association, and this work focused on only 1 direction. However, the study design was appropriate for assessing the longitudinal associations of depression and anxiety with the accumulation of chronic conditions. The most rapid accumulation of chronic conditions was consistently observed with comorbid depression and anxiety; however, significant additive or multiplicative synergistic interactions between depression and anxiety were not observed. The etiologic complexities of depression, anxiety, and the somatic conditions under consideration in this study may conform poorly to simple additive or multiplicative statistical associations. Our exposure and outcome definitions relied on data not collected for research purposes, and it is unclear how much the higher rates of chronic conditions among individuals with mental health conditions reflects differences in health care service utilization (resulting in accruing more diagnosis billing codes) vs greater incidence. Although the REP captures virtually the entire local Olmsted County, Minnesota, population compared with the US Census, some individuals with depression in the population may have been misclassified as being nondepressed, especially because diagnoses of depressive disorders may be missed in routine care settings. We did not include personality disorders in our definition of depression or anxiety, which is an important limitation, given that many personality disorders are difficult to differentiate from affective disorders, prevalent among individuals seeking health care services, and associated with higher morbidity and mortality compared with individuals without personality disorders. Our list of accumulated chronic conditions was limited to 15 conditions, and the actual dates of onset likely occurred before the estimated dates of onset using diagnosis codes. The risk of reverse causation bias (eg, indolent diseases increasing the risk of depression and anxiety) was minimized by the use of Anderson-Gill models that accounted only for new conditions but cannot be completely excluded, given the use of diagnosis codes to define the onset dates of conditions. Additionally, the generalizability of our results may be limited for populations more economically or racially diverse than our study cohort.

Conclusions
In this cohort study of men and women from 3 birthday age cohorts, the risk of accumulating chronic conditions was increased in women with depression and comorbid depression-anxiety across the age span and in younger men. Compared with individuals without depression or anxiety, there was a higher rate of accumulation of comorbid conditions when depression and anxiety cooccurred among women across the age spectrum and among younger men.
Clinic, Rochester, Minnesota (St Sauver, Rocca); The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota (St Sauver); Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland (Boyd); Department of Neurology, Mayo Clinic, Rochester, Minnesota (Rocca); Women’s Health Research Center, Mayo Clinic, Rochester, Minnesota (Rocca).

Author Contributions: Dr Bobo and Mr Grossardt had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Bobo, Grossardt, St Sauver, Rocca.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bobo, Grossardt, Virani.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Grossardt.

Obtained funding: St Sauver, Rocca.

Administrative, technical, or material support: Virani, Rocca.

Supervision: Bobo.

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Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content of this article is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health (NIH) or the Mayo Clinic.

REFERENCES


**SUPPLEMENT.**

eTable 1. List of the Diagnosis Codes Used to Define Depression and Anxiety

eTable 2. List of Chronic Conditions and Corresponding Diagnosis Codes

eTable 3. Risk of Death in Birthday Age Cohorts for Women and Men Separately

eFigure 1. Inclusion of Individuals in Birthday Age Cohorts and Accumulation of Chronic Conditions

eFigure 2. Balance of Characteristics by Birthday Age Cohort

eFigure 3. Kaplan-Meier Estimates of Mortality in the Age 60 Years Cohort Separately for Women and Men