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Complete List of Authors:	St Sauver, Jennifer; Mayo Clinic, Health Sciences Research Boyd, Cynthia; Johns Hopkins University, Geriatric Medicine and Gerontology Grossardt, Brandon; Mayo Clinic, Biomedical Statistics and Informatics Bobo, William; Mayo Clinic, Department of Psychiatry Finney Rutten, Lila; Mayo Clinic, The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery Roger, Verinique; Mayo Clinic, The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery Ebbert, John; Mayo Clinic, The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery Therneau, Terry; Mayo Clinic, Biomedical Statistics and Informatics Yawn, Barbara; Olmsted Medical Center, Research Rocca, Walter; Mayo Clinic, Health Sciences Research
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Risk of developing multimorbidity across all ages in a cohort study: differences by sex and ethnicity

Jennifer L. St. Sauver *associate professor* [1 2], Cynthia M. Boyd *associate professor* [3], Brandon R. Grossardt *biostatistician* [4], William V. Bobo *assistant professor* [5], Lila J. Finney Rutten *associate professor* [1 2], Véronique L. Roger *professor* [1 2 6], Jon O. Ebbert *professor* [2], Terry M. Therneau *professor* [4], Barbara P. Yawn *director of research* [1 7], Walter A. Rocca *professor* [1 8]

Author Affiliations: [1] Divisions of Epidemiology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [2] The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [3] Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287, USA; [4] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [5] Department of Psychiatry and Psychology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [6] Division of Cardiovascular Diseases, Department of Internal Medicine, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [7] Department of Research, Olmsted Medical Center, 210 Ninth Street SE, Rochester, MN 55904, USA; [8] Department of Neurology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

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Corresponding Author: Walter A. Rocca, MD, MPH, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (telephone: 507-284-3568; fax: 507-284-1516; e-mail: rocca@mayo.edu).

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ABSTRACT

Objective: To study the incidence of de novo multimorbidity across all ages in a geographically defined population with an emphasis on sex and ethnic differences.

Design: Historical cohort study.

Setting: All persons residing in Olmsted County, Minnesota, USA on January 1, 2000 who had not refused permission for their records to be used for research (n = 123,716).

Participants: We used the Rochester Epidemiology Project medical records-linkage system to identify all of the county residents. We identified and removed from the cohort all persons who had developed multimorbidity before January 1, 2000 (baseline date), and we followed the cohort over 14 years (January 1, 2000 through December 31, 2013).

Main outcome measures: Incident multimorbidity was defined as the development of the second of 2 conditions (dyads) from among the 20 chronic conditions selected by the United States Department of Health and Human Services. We also studied the incidence of the third of 3 conditions (triads) from among the 20 chronic conditions.

Results: The incidence of multimorbidity increased steeply with older age; however, the number of people with incident multimorbidity was substantially greater in those younger than 65 years compared to people age 65 years or older (28,378 vs. 6,214). The

overall risk was similar in men and women; however, the combinations of conditions (dyads and triads) differed extensively by age and by sex. Compared to Whites, the incidence of multimorbidity was higher in Blacks and lower in Asians.

Conclusions: The risk of developing de novo multimorbidity increases steeply with older age, varies by ethnicity, and is similar in men and women overall. However, the combinations of conditions vary extensively by age and sex. These data represent an important first step toward identifying the causes and the consequences of multimorbidity.

ARTICLE SUMMARY: Strengths and limitations of this study

- This is one of the first studies worldwide focusing on the incidence of multimorbidity rather than on the prevalence of multimorbidity. Prevalence reflects both the effect of incidence and of survival after the onset of multimorbidity. We used a simple definition of incident multimorbidity that can be replicated in other populations.
- This study covered an entire geographically defined population, and used a unique records-linkage system. Therefore, the study used 19 years of data accumulation in medical records. None of the data were derived from self-report or interviews.
- Studies of multimorbidity require the definition of the number of conditions considered, of the time window of occurrence, and of the source of data (medical records vs. interview). We used the 20 conditions recommended by the US Department of Health and Human Services. These 20 conditions represent a first consensus list; however, not all of the conditions have the same impact on the complexity of care or on the quality of life of patients.
- Potential weaknesses of this study include the uncertain validity of diagnostic codes, the possible incompleteness of information due to in or out migration, and the inability to generalize our findings to other populations with different demographic or social characteristics.
- Replication of this study in other populations in the United States and worldwide will allow for useful comparisons.

INTRODUCTION

The demographic expansion of the elderly population and the improvements in survival of people affected by chronic conditions have caused a dramatic rise in the number of people living with multimorbidity (≥ 2 chronic conditions). In the United States, the prevalence of multimorbidity among Medicare recipients increases from 62% at age 65 - 74 years to 82% at ages 85 years and older. [1] The monetary costs associated with managing patients with multiple chronic conditions are overwhelming. [2-4] In addition, fragmented health care in patients with multimorbidity causes a particularly high risk for complications and a lower quality of life. [5,6]

Several studies have described the prevalence of multimorbidity in a wide range of populations. [1,7-12] Additional studies have focused on how to manage patients with multiple chronic conditions. [13,14] However, in 2010 the United States Department of Health and Human Services (US-DHHS) highlighted the critical need to identify groups of individuals at higher risk of developing multimorbidity (first appearance of multimorbidity). Such studies of incident multimorbidity are essential to identify patterns of disease accumulation, and to identify the populations at high risk of developing multimorbidity. For example, multimorbidity is highly prevalent in the elderly; however, many of the processes that lead to multimorbidity begin at much earlier ages. Therefore, data on the ages at which multimorbidity begins and on the patterns of accumulation of conditions over time are urgently needed to develop focused interventions to prevent multimorbidities and their adverse health outcomes. [15]

Unfortunately, there are currently no population-based data on the incidence of multimorbidity in the United States across all ages, even though multimorbidity is a high

public health priority for the nation. [15] The Rochester Epidemiology Project (REP) medical records-linkage system captures long-term medical information on a stable population, and is therefore uniquely positioned to study the incidence of multimorbidity. In a previous paper, we described in detail the patterns of prevalent multimorbidity in this population. [16] In this study, we further leveraged this data resource to examine the incidence of multimorbidity across all ages, separately in men and women, and in three ethnic groups. [17]

METHODS

Study population

The REP has tracked and linked health care information for the population of Olmsted County, MN, since 1966.[17-19] The vast majority of medical care in this community is currently provided by a few health care institutions: Olmsted Medical Center and its affiliated hospital, Mayo Clinic and its two affiliated hospitals, the Rochester Family Medicine Clinic, and a few smaller care facilities. The health care records from these institutions are linked together through the REP records-linkage system. [17-19] Persons are considered residents of Olmsted County at the time of each health care visit based on their address. Over the years, this address information has been accumulated and is used to define who resided in Olmsted County at any given point in time since 1966 (REP Census). The population counts obtained by the REP Census are similar to those obtained by the US Census, indicating that virtually the entire population of the county is captured by the system. [18-20] We used the REP Census to identify all individuals who resided in Olmsted County on January 1, 2000 (baseline date); however, we included

only individuals who had not refused permission to use their medical records for research (Minnesota research authorization). [18,21,22]

Definition of incident multimorbidity

We focused on 20 selected chronic conditions recommended by the US-DHHS for studying multimorbidity. [23,24] The list of the 20 conditions and the corresponding ICD-9 codes used in this study are provided in Supplementary Table A. [23,2423,24] We first identified all ICD-9 codes associated with these 20 chronic conditions that occurred in the population between January 1, 1995 and December 31, 1999 (5 years before the baseline date, January 1, 2000). Persons who did not have any ICD-9 code for a given condition were assumed to not have the condition of interest. By contrast, residents were defined as having a chronic condition if they had at least two ICD-9 codes for that condition separated by more than 30 days, and the incidence date was assigned at the time they received a second diagnostic code.

Persons who had 2 or more of the 20 conditions at baseline were considered to have prevalent multimorbidity and were therefore excluded from incidence analyses of 2 chronic conditions (dyads). Similarly, persons who had 3 or more of the 20 conditions at baseline were excluded from incidence analyses of 3 chronic conditions (triads). All persons in this fixed population cohort were followed historically through the REP records-linkage system for approximately 14 years to study the emergence of new conditions.

Statistical Analyses

All persons in the cohort were followed from January 1, 2000 through the last contact with the records-linkage system (the earliest of death date, last medical visit date, or December 31, 2013). The incidence of each of the 20 chronic conditions was calculated among persons free of that condition at baseline. Persons contributed person-years to the denominator for the incidence of 2 conditions (development of a second condition in a dyad) only during the time when they had 0 or 1 chronic conditions, whereas persons contributed person-years to the denominator for the incidence of 3 chronic conditions (development of a third condition in a triad) only when they had 0, 1, or 2 chronic conditions. Although the majority of people accumulated conditions one-at-a-time, some subjects jumped from 0 to 2 conditions, or from 1 to 3, or even from 0 to 3 conditions. For example, a person previously considered free of all of the 20 conditions who was diagnosed with hyperlipidemia, hypertension, and depression during one visit was counted both as an incident dyad and as an incident triad on the same date.

Incidence rates were reported separately by age (using seven age strata or splitting the entire population in 0-64 and ≥ 65 years), sex, and ethnicity, and were directly standardized by age and sex to the total US 2010 Decennial Census after removing projected prevalence (see Supplementary Table B). Because the study covered the target population completely, and no sampling was involved, confidence intervals were not included in the tables. [25 26] Ethnicity data were not available for 9,176 people (7.4% of the cohort). These individuals were included in the overall and age- and sex-specific analyses, but not in the ethnicity-specific analyses.

Although the 20 conditions proposed by the US-DHHS represent a national consensus, [15] some of the conditions may have a different prognostic impact than others. For example, hyperlipidemia and hypertension often occur together and tend to remain asymptomatic. Therefore, we performed a set of sensitivity analyses combining hyperlipidemia and hypertension as a single chronic condition. The date of incidence for the single chronic condition of hyperlipidemia and/or hypertension was defined as the date the person first met criteria for either of these conditions.

RESULTS

Description of the Olmsted County population

The REP Census identified 129,311 Olmsted County, MN residents on January 1, 2000 compared with 124,277 individuals counted by the 2000 US Census (104.1%); 123,716 persons provided Minnesota research authorization for medical record research (95.7%) and were included in our analyses. A total of 17,655 people (14.3%) had 2 or more conditions at the baseline date and 9,368 (7.6%) had 3 or more conditions (prevalent multimorbidity). Overall, we observed a total of 1,334,906 person-years of follow-up, but the length of follow-up varied by age group. For example, median follow-up was 13.1 years in persons aged 0 to 19 years at baseline, 12.3 years in persons aged 70 to 79 years at baseline, and 4.9 years in persons aged 80 years or older at baseline.

Figure 1 and Supplementary Table C report the incidence of each of the 20 chronic conditions considered separately by age and sex. The incidence of most of the chronic conditions increased steeply with older age. However, the incidence of asthma, substance abuse disorders, hepatitis, autism spectrum disorder, and infection with

human immunodeficiency virus was higher in the younger population compared to those older than 60 years. The incidence of depression increased from ages 0-19 to 20-39 years, declined from 40-49 to 60-69 years, and increased sharply again thereafter. The incidence of most conditions was higher in men compared to women of the same age; however, women had a higher incidence of depression, arthritis, asthma, and osteoporosis. The incidence curves in men and women crossed at age 50-59 years for cancer and at age 60-69 years for chronic obstructive pulmonary disease (Figure 1).

Incidence of multimorbidity by age, sex, and ethnicity

Figure 2 shows the age-specific incidence rates of multimorbidity in men and women separately (panels A and C), and in three ethnic groups (panels B and D). Both the incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased steeply with older age (Table 1, Table 2, and Figure 2). For example, the incidence of 2 chronic conditions in men was 6.5/1,000 person-years in persons who were ages 0-19 years, and 260.0/1,000 in persons who were ≥ 80 years. The overall incidence of 2 chronic conditions was slightly higher in women compared to men (overall standardized incidence rates 38.8 vs. 35.5/1,000 person-years; Table 1). The incidence of 2 chronic conditions was higher in Blacks compared to Whites, but lower in Asians compared to Whites (standardized incidence rates; Table 1 and Figure 2). We observed similar patterns for the development of 3 chronic conditions (Table 2 and Figure 2). The overall incidence of 3 conditions was similar in men and women (standardized incidence rates 25.5/1,000 person-years in men vs. 26.6/1,000 person-years in women); however, it was higher in Blacks and lower in Asians, compared to Whites (Figure 2).

In the set of sensitivity analyses in which we combined hyperlipidemia and hypertension as a single condition, we observed a slight decrease in the incidence of 2 chronic conditions and of 3 chronic conditions compared with the primary analyses. The overall incidence rate of 2 conditions decreased from 35.0 to 34.0/1,000 person-years in men and from 40.3 to 40.0/1,000 person-years in women. The incidence rate of 3 conditions decreased from 24.7 to 22.5/1,000 person-years in men and from 28.5 to 27.0/1,000 person-years in women (incidence rates non-standardized; data not shown in the Tables). For both 2 and 3 conditions, the decrease in incidence was more sizeable in men than in women.

Incidence of dyads and triads

Table 3 shows the incidence of the most common dyads or triads of chronic conditions in seven age strata and for men and women separately. The incidence of dyads and triads varied extensively with age. For example, the most common incident dyad in persons 0-19 years was depression and asthma (1.8/1,000 person-years in boys or men and 2.9/1,000 person-years in girls or women). By comparison, the most common dyad in persons ≥ 80 years was hypertension and cancer in men (18.9/1,000 person-years) and hypertension and arthritis in women (27.7/1,000 person-years). Similarly, the most common incident triad of conditions in persons aged 0-19 years was depression, asthma, and substance abuse disorders in both sexes. By comparison, the most common incident triads in persons ≥ 80 years were hypertension, cancer, and arrhythmia in men and hyperlipidemia, hypertension, and arthritis in women.

The incidence of dyads and triads also varied by sex. In some instances, the composition of the dyads or triads was the same for men and women, but the magnitude of the incidence rate was different. In other instances, the magnitude of the incidence rate was similar in men and women, but the composition of the dyads and triads varied by sex. For example, the most common incident dyad in persons aged 60-69 years was hyperlipidemia and hypertension in both sexes, but the incidence rate was higher in men compared to women (23.4/1,000 person-years vs. 18.8/1,000 person-years). By contrast, the incidence rates of the most common triads in persons aged 60-69 years were similar in men and women (11.6/1,000 vs. 10.3/1,000 person-years); however, they included different conditions (Table 3).

DISCUSSION

Statement of the principal findings

The burden of multimorbidity in the United States is high and is increasing with an aging population and with improvements in survival. We leveraged a unique longitudinal data resource covering an entire stable and geographically defined population to examine the incidence of multimorbidity across all ages. The incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased steeply with older age, and the overall risk was similar in men and women. However, the number of people who developed multimorbidity before age 65 was more than four times greater than the number of people who developed multimorbidity after age 65. The incidence of multimorbidity was highest in Blacks, and lowest in Asians. Finally, the combinations of conditions in incident dyads and triads differed extensively by age and by sex. These

results have important implications for identifying individuals at higher risk of developing multimorbidity at different ages. These data are also a first step toward understanding the causes and the consequences of multimorbidity.

Strengths and weaknesses

A unique strength of our study was the ability to measure the incidence of multimorbidity documented in medical records across seven age groups and for an entire, geographically defined population. We used historical data both to exclude individuals with prevalent multimorbidity at baseline and to follow individuals over a long period of time to accurately document the development of incident multimorbidity. In total, our findings reflect 19 years of data accumulation (5 years before and 14 years after the baseline date).

Unfortunately, there is no standard definition of multimorbidity. Previous studies have included a wide range of chronic conditions and a wide range of time frames. We defined multimorbidity using the 20 conditions selected by US-DHHS which were chosen because they "meet the definition for chronicity, are prevalent [common], and are potentially amenable to public health or clinical interventions or both." [23] However, this definition provides equal weight to each of the 20 conditions without considering the impact of combinations of specific conditions on the quality of life of patients, the complexity of their joint management, and the severity of their long-term outcomes.

Some of the dyads and triads derived by the combination of the 20 conditions selected by the US-DHHS may have a much stronger impact on the complexity of clinical management than others. [27] Therefore, some dyads or triads may be

particularly costly for the health system, harder for the patient to manage by themselves, less amenable to a single disease approach to care (e.g., telemonitoring for heart failure), and may have a stronger effect on functionality, severity of symptoms, and risk of death. In addition, social (e.g., inadequate insurance, low education) and behavioral factors (e.g., poor diet) not reflected in the list of 20 US-DHHS conditions may be as important, or more important, than the 20 conditions in determining the complexity of clinical management and long-term outcomes. [27]

For example, because hyperlipidemia and hypertension are typically asymptomatic, and are often diagnosed as the result of routine screening, their combination is likely to have a much lower impact on the life of the patient than the combination of schizophrenia and heart failure. However, both combinations are considered multimorbidity by the US-DHHS definition. Our sensitivity analyses highlight this problem. As expected, when hyperlipidemia and hypertension were considered as a single condition, the overall incidence of multimorbidity decreased. The decreases were relatively small but were more sizeable in men than in women. These findings emphasize the importance of reaching consensus on the list of conditions to be used to define multimorbidity. However, it is difficult to assess the utility of the 20 conditions included in the US-DHHS list without also understanding how different combinations of these conditions impact long term outcomes. Therefore, we plan to continue this initial incidence study with further analyses to assess which combinations of conditions have the greatest impact on adverse outcomes, including patient quality of life and complexity of clinical management. [27]

We defined incident multimorbidity as the date on which a person met the criteria for a second condition or for a third condition. We used an approach similar to that used in the definition for the onset of metabolic syndrome (reaching three of five components of the syndrome). [28,29] This simple operational definition of incident multimorbidity should be easy to replicate, and should facilitate future comparisons with other populations.

Potential weaknesses of our study include the inability to validate the ICD-9 codes. It was not possible to confirm all diagnoses for the entire study population, and some ICD-9 codes may have been assigned in error (e.g., "rule out" diagnostic codes). To reduce the likelihood of a single ICD-9 code error, we required two or more diagnosis codes separated by more than 30 days for a person to be defined as having a condition. [30] However, if a person received a valid code and was lost to follow-up or died rapidly after diagnosis, we may have underestimated the incidence of some of the conditions. In addition, we used diagnosis date as a proxy for the true date of onset of the condition.

Some individuals may have moved into Olmsted County after having been diagnosed with one or more chronic conditions elsewhere. If those persons continued to receive care within the REP for a number of years, we captured their chronic condition at the time of subsequent health care visits. However, we did not know the true date of onset for the condition, and the sequence of accumulation of conditions could be distorted. Because the population of Olmsted County is stable, particularly among persons who are 40 years of age or older, [19] we do not expect a major distortion of multimorbidity incidence rates due to migration.

Finally, our study focused on a single geographically defined US population, and the incidence of multimorbidity may differ in other populations. However, the demographic and socioeconomic characteristics of our population are similar to those of the upper Midwest of the United States,[20] and the prevalence of multimorbidity in persons 65 years of age or older was similar in our population compared with the entire US Medicare population. [16] Replication of this study in other populations in the United States and worldwide will allow for useful comparisons.

Comparison with other studies

A number of studies have described the prevalence of multimorbidity in various populations; [1,7-12] however, few studies have described the incidence of multimorbidity, and no incidence studies are available for the US. In 1998, Van den Akker and colleagues estimated the one year incidence of multimorbidity in patients from a network of family practices in the Netherlands. [31] Incident multimorbidity was defined as the new development of at least 2 of 335 diagnostic categories within a one year period. Overall, 7.9% of their population developed one new disease and 1.3% developed two or more new diseases in one year. The proportion of people who developed two or more new conditions increased with older age, but did not differ substantially by sex. It is difficult to compare our results directly to the Dutch findings because of methodological differences (e.g., number of conditions considered and time frame), and because it is not clear whether some of the participants in the Dutch study already had one or more conditions at baseline. However, we observed similar patterns of

increasing incidence with older age, and limited differences between men and women in overall incidence.

More recently, Melis and colleagues assessed the incidence of multimorbidity in Swedish people aged 75 years or older at baseline who participated in a longitudinal cohort study. [32] Incident multimorbidity was defined as the development of at least 2 of 39 chronic conditions during three years of follow-up. Participants with none of the 39 chronic conditions at baseline had a multimorbidity incidence rate of 12.6 per 100 person-years, and patients with one of the 39 conditions at baseline had an incidence rate of 32.9 per 100 person-years. Although we examined fewer conditions than the Swedish group (20 vs. 39), and the ascertainment of incident conditions was different (medical records data vs. survey methods), our incidence rates of multimorbidity in subjects aged 75 years or older were similar (19.1 per 100 person-years in people with no conditions at baseline and 38.9 per 100 person-years in persons with one condition at baseline; both sexes combined; data not shown).

Meaning of the study

To understand the importance of these findings, we draw an analogy with the difference between prevalence and incidence in epidemiologic studies considering one disease at a time. [33,34] Incidence is the direct measure of the risk of people to develop a given disease, whereas prevalence is the percent of people affected by the same disease at one point in time, and reflects both the effect of incidence and the effect of survival after the onset of the disease. [33,34] Similarly, the prevalence of multimorbidity gives us a static picture of the population; however, prevalence may be misleading when studying

the mechanisms of multimorbidity. For example, a higher prevalence of multimorbidity in women than in men may be due to a higher risk of women developing multimorbidity, or to a longer survival of women affected by multimorbidity. [16] By contrast, a higher incidence of multimorbidity in women compared to men points directly to a difference in risk (assuming that access to care is comparable in the sexes).

Prior studies of the prevalence of multimorbidity have shown a dramatic increase in the number of people living with 2 or more chronic conditions at older ages. [1,7-11] However, the high prevalence of multimorbidity in the older population implies that relatively few older individuals remain at risk of developing multimorbidity. Overall, among persons aged ≥ 80 years at baseline, only 891 out of 3,710 (24.0%) were at risk of developing 2 chronic conditions (the other 76.0% already had 2 or more of the 20 conditions). Therefore, the persons who reached 80 years of age or older and remained free of multimorbidity represent an ideal population in which to study successful aging and resiliency.

We also found that the total number of people who developed multimorbidity before age 65 years was more than 4 times greater than the number of people who developed multimorbidity at age 65 or older (28,378 vs. 6,214). These data emphasize the need to target preventive efforts at much younger ages, but represent only a first step toward future research to identify the social, behavioral, and clinical risk and protective factors for multimorbidity.

We found important differences in the incidence of multimorbidity by ethnicity. The age standardized incidence rates of multimorbidity were higher in Blacks and lower in Asians compared to Whites. Our findings are consistent with previous studies that

showed a higher prevalence of multimorbidity in Blacks compared to Whites, but a lower prevalence of multimorbidity in Asians. [8,16,35-37] Our data suggest that some of these differences in prevalence may be attributed to differences in the incidence of the conditions among different ethnic groups. However, differential survival may also contribute to the differences in prevalence, which, in turn, may be influenced by socioeconomic factors, lifestyle behaviors, social environment, and healthcare access. Further research is needed to better characterize these disparities and to identify the causal mechanisms that contribute to different development of chronic conditions and to different survival.

The incidence and the composition of the dyads and triads of conditions varied extensively across age and sex strata. For example, women 20 years of age or older were more likely to have depression as a component of their incident multimorbidity dyads and triads compared to men. Such differences may lead to different long-term outcomes in men and women. Therefore, these data are useful to understand how multimorbidity develops, and are an important first step toward future research. In particular, such incident data are necessary to study the chronological order of acquisition of multiple chronic conditions in different age, sex, and ethnic strata. Incidence data are also necessary to determine whether the differential order of acquisition is associated with a different risk of adverse long-term outcomes such as hospitalizations, emergency department visits, or death. For example, it is not clear whether acquiring depression prior to arthritis results in worse long-term outcomes compared with acquiring arthritis prior to depression. Future studies are also needed to

understand how additional chronic conditions accumulate after the development of a second and third condition.

Conclusions and clinical implications

It is important and urgent to understand the causes and the consequences of multimordibity to inform efforts to delay and prevent disease onset and to develop effective strategies for caring for patients with multimorbidity. We studied the incidence of multimorbidity across all ages, separately in men and women, and in three ethnic groups in a geographically defined US population. The incidence of multimorbidity increased dramatically with older age and was higher in Blacks but lower in Asians compared to Whites. Men and women had a similar overall risk, but the combinations of conditions within dyads and triads varied extensively by age and by sex. These data represent an important first step toward identifying specific risk factors for multimorbidity, understanding how chronic conditions accumulate over time, and toward identifying individuals at highest risk of adverse outcomes.

Competing interest declaration:

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have support from any companies for the submitted work; (2) none of the authors have any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have any non-financial interests that may be relevant to the submitted work.

Contributorship statement: Dr. St. Sauver had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor for the study.

Study concept and design: St. Sauver, Boyd, Grossardt, Yawn, Rocca.

Acquisition, analysis, or interpretation of data: St. Sauver, Grossardt, Rocca.

Drafting of the manuscript: St. Sauver, Rocca.

Critical revision of the manuscript for important intellectual content: St. Sauver, Boyd, Grossardt, Bobo, Finney Rutten, Roger, Ebbert, Therneau, Yawn, and Rocca.

Statistical analysis: Grossardt, Therneau.

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Study supervision: Yawn, Rocca.

Identifiable patients: No identifiable patients were included.

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Transparency declaration: The lead author (the manuscript's guarantor, Dr. JLS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1. Incidence of the second of two chronic conditions (per 1,000 person-years) in persons living in Olmsted County, MN by age, sex, and ethnicity.

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
All ethnic groups						
0-19	18,879	140,653	6.5 (921)	18,024	134,725	8.5 (1,151)
20-39	27,732	151,734	17.2 (2,613)	28,571	158,252	25.1 (3,972)
40-49	16,396	82,324	43.6 (3,590)	16,713	85,660	45.8 (3,920)
50-59	11,779	52,085	85.2 (4,436)	12,398	55,270	84.6 (4,674)
60-69	5,218	19,653	139.4 (2,739)	5,603	21,246	135.3 (2,874)
70-79	1,775	5,451	209.9 (1,144)	2,184	6,660	202.0 (1,345)
≥ 80	531	1,589	260.0 (413)	1,016	2,887	277.1 (800)
0-64	50,648	439,254	29.7 (13,059)	51,056	447,399	34.2 (15,319)
≥ 65	3,794	14,236	196.5 (2,797)	4,636	17,300	197.5 (3,417)
All ages	52,479	453,489	35.0 (15,856)	53,582	464,699	40.3 (18,736)
Standardized†	---	---	35.5	---	---	38.8
Blacks						
0-19	877	6,411	5.5 (35)	749	5,362	6.0 (32)
20-39	1,099	6,178	16.5 (102)	934	5,647	23.0 (130)
40-49	429	1,836	63.2 (116)	324	1,392	61.8 (86)
50-59	180	683	105.3 (72)	139	513	121.0 (62)
60-69	60	223	134.8 (30)	47	150	193.2 (29)
70-79	18	71	140.1 (10)	23	60	200.4 (12)
≥ 80	4	11	274.0 (3)	3	5	580.3 (3)
0-64	1,848	15,240	22.0 (335)	1,563	13,010	25.5 (332)
≥ 65	48	173	190.8 (33)	37	118	185.7 (22)
All ages	1,873	15,413	23.9 (368)	1,587	13,128	27.0 (354)
Standardized†	---	---	38.9	---	---	48.5
Asians						
0-19	818	6,331	3.5 (22)	826	6,299	5.6 (35)
20-39	1,090	6,372	15.1 (96)	1,168	7,167	14.6 (105)
40-49	534	2,464	39.8 (98)	591	2,869	33.8 (97)
50-59	339	1,588	71.8 (114)	376	1,687	79.4 (134)
60-69	159	592	120.0 (71)	185	570	161.3 (92)
70-79	51	163	140.8 (23)	74	177	271.6 (48)
≥ 80	21	60	216.6 (13)	40	92	358.1 (33)
0-64	1,897	17,137	21.6 (370)	1,997	18,399	23.3 (429)
≥ 65	114	433	154.7 (67)	159	463	248.4 (115)
All ages	1,954	17,571	24.9 (437)	2,105	18,862	28.8 (544)
Standardized†	---	---	29.5	---	---	34.9
Whites						
0-19	14,956	119,686	6.8 (818)	14,414	114,906	9.0 (1,032)
20-39	21,792	128,801	17.9 (2,303)	23,214	135,903	26.5 (3,599)
40-49	14,426	74,921	43.6 (3,269)	15,088	79,123	46.1 (3,646)
50-59	10,795	48,361	85.8 (4,149)	11,520	51,901	84.8 (4,399)

Table 1. Continued

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
60-69	4,823	18,362	140.4 (2,578)	5,221	20,075	134.7 (2,704)
70-79	1,653	5,090	212.6 (1,082)	2,030	6,301	200.9 (1,266)
≥ 80	497	1,495	262.8 (393)	953	2,754	274.5 (756)
0-64	40,703	383,410	31.2 (11,952)	42,149	394,566	35.9 (14,170)
≥ 65	3,517	13,306	198.4 (2,640)	4,317	16,398	197.1 (3,232)
All ages	42,382	396,716	36.8 (14,592)	44,465	410,964	42.3 (17,402)
Standardized†	---	---	36.0	---	---	39.4

* Incidence rates are reported per 1,000 person-years.
† Incidence rates were directly standardized to the total US population from the 2010 US Decennial Census after removing the number of people with prevalent multimorbidity (≥ 2 chronic conditions) as projected from our previous study (see Supplementary Table B).[16]

Table 2. Incidence of the third of three chronic conditions (per 1,000 person-years) in persons living in Olmsted County, MN by age, sex, and ethnicity.

	Men			Women		
Ethnicity age (years)	**Persons**	**Person-years**	**Incidence rate* (n)**	**Persons**	**Person-years**	**Incidence rate* (n)**
All ethnic groups						
0-19	19,029	144,025	1.3 (186)	18,203	138,055	2.0 (282)
20-39	28,721	162,693	6.9 (1,123)	30,135	177,878	10.9 (1,944)
40-49	17,901	95,582	22.6 (2,157)	18,824	103,400	24.2 (2,507)
50-59	14,398	69,907	52.8 (3,688)	15,475	76,247	51.5 (3,930)
60-69	7,517	31,617	99.5 (3,146)	8,313	35,342	96.7 (3,416)
70-79	3,109	10,639	169.7 (1,805)	3,899	13,653	156.4 (2,136)
≥ 80	992	3,230	218.9 (707)	1,970	6,414	230.6 (1,479)
0-64	53,073	491,536	18.0 (8,852)	54,280	517,164	20.2 (10,432)
≥ 65	5,938	26,156	151.4 (3,960)	7,706	33,825	155.6 (5,262)
All ages	55,898	517,693	24.7 (12,812)	58,450	550,989	28.5 (15,694)
Standardized†	---	---	25.5	---	---	26.6
Blacks						
0-19	879	6,530	1.1 (7)	751	5,458	1.1 (6)
20-39	1,123	6,428	8.6 (55)	960	6,032	9.4 (57)
40-49	460	2,126	34.8 (74)	373	1,723	41.2 (71)
50-59	218	952	69.3 (66)	173	737	69.2 (51)
60-69	81	312	96.1 (30)	70	241	132.8 (32)
70-79	27	108	129.4 (14)	28	84	191.0 (16)
≥ 80	5	23	172.3 (4)	5	9	321.2 (3)
0-64	1,883	16,227	13.3 (216)	1,602	14,101	14.5 (205)
≥ 65	58	252	135.1 (34)	54	183	169.2 (31)
All ages	1,911	16,479	15.2 (250)	1,633	14,284	16.5 (236)
Standardized†	---	---	28.2	---	---	34.8
Asians						
0-19	823	6,419	0.6 (4)	832	6,442	1.6 (10)
20-39	1,109	6,747	6.2 (42)	1,206	7,587	4.6 (35)
40-49	574	2,841	18.7 (53)	651	3,327	20.7 (69)
50-59	390	1,942	44.8 (87)	439	2,191	46.1 (101)
60-69	203	830	78.3 (65)	254	966	97.3 (94)
70-79	80	259	138.8 (36)	110	353	141.5 (50)
≥ 80	32	84	202.0 (17)	84	228	241.2 (55)
0-64	1,940	18,472	12.2 (225)	2,074	20,167	12.9 (261)
≥ 65	165	650	121.5 (79)	258	929	164.7 (153)
All ages	2,027	19,122	15.9 (304)	2,235	21,096	19.6 (414)
Standardized†	---	---	21.1	---	---	23.2
Whites						
0-19	15,088	122,717	1.3 (160)	14,576	117,885	2.2 (259)
20-39	22,681	138,725	7.1 (990)	24,638	154,160	11.7 (1,799)
40-49	15,811	87,199	22.7 (1,978)	17,025	95,693	24.1 (2,308)
50-59	13,262	65,243	53.1 (3,464)	14,443	71,770	51.7 (3,714)

Table 2. Continued

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
60-69	7,028	29,816	100.8 (3,005)	7,796	33,477	96.9 (3,244)
70-79	2,930	10,061	171.9 (1,729)	3,680	13,006	157.2 (2,045)
≥ 80	942	3,093	219.5 (679)	1,848	6,105	231.0 (1,410)
0-64	42,953	432,089	19.0 (8,213)	45,157	459,919	21.2 (9,761)
≥ 65	5,572	24,764	153.1 (3,792)	7,224	32,177	155.9 (5,018)
All ages	45,583	456,853	26.3 (12,005)	49,033	492,097	30.0 (14,779)
Standardized†	---	---	25.7	---	---	27.0

* Incidence rates are reported per 1,000 person-years.
† Incidence rates were directly standardized to the total US population from the 2010 US Decennial Census after removing the number of people with prevalent multimorbidity (≥ 3 chronic conditions) as projected from our previous study (see Supplementary Table B).[16]

Table 3. Incidence rates (per 1,000 person-years) and composition of the most common dyads and triads of chronic conditions in persons living in Olmsted County, MN by age and sex.

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
0 – 19								
1	DEP - AST	1.8 (257)	DEP - AST	2.9 (395)	DEP - AST - SUB	0.4 (53)	DEP - AST - SUB	0.4 (62)
2	DEP - SUB	1.3 (178)	DEP - SUB	1.8 (240)	DEP - AST - COPD	0.1 (17)	DEP - AST - COPD	0.3 (39)
3	AST - COPD	0.9 (122)	AST - COPD	0.7 (91)	DEP - SUB - SZO	0.1 (8)	DEP - ARR - AST	0.2 (27)
4	AST - SUB	0.4 (56)	DEP - ARR	0.4 (50)	LIP - DEP - AST	<0.1 (7)	DEP - ARR - SUB	0.1 (13)
5	DEP - ARR	0.1 (21)	DEP - COPD	0.4 (48)	3-way tie ‖	< 0.1 (6)	DEP - SUB - COPD	0.1 (12)
20 – 39								
1	DEP - SUB	3.5 (525)	DEP - AST	3.4 (531)	DEP - AST - SUB	0.4 (73)	DEP - AST - SUB	0.8 (134)
2	LIP - HTN	1.4 (207)	DEP - SUB	2.9 (463)	DEP - SUB - SZO	0.4 (69)	DEP - AST - COPD	0.7 (121)
3	DEP - AST	1.1 (174)	DEP - CAN	2.0 (309)	LIP - HTN - DIA	0.4 (65)	DEP - ARR - AST	0.4 (77)
4	LIP - DEP	1.0 (155)	LIP - DEP	1.7 (267)	DEP - ARR - SUB	0.3 (46)	DEP - SUB - COPD	0.3 (61)
5	LIP - DIA	0.9 (137)	DEP - ARR	1.4 (222)	LIP - HTN - DEP	0.3 (45)	LIP - DEP - AST	0.3 (58)
40 – 49								
1	LIP - HTN	7.0 (580)	LIP - DEP	4.1 (354)	LIP - HTN - DIA	3.1 (294)	LIP - HTN - DIA	1.4 (147)
2	LIP - DIA	4.4 (363)	LIP - HTN	3.6 (308)	LIP - HTN - DEP	1.2 (115)	LIP - HTN - DEP	1.1 (114)
3	LIP - DEP	3.5 (285)	DEP - ART	2.6 (224)	LIP - HTN - ART	0.9 (84)	LIP - DEP - DIA	1.0 (99)
4	LIP - ART	2.4 (198)	DEP - CAN	2.6 (224)	LIP - HTN - CAD	0.9 (83)	LIP - DEP - ART	0.8 (84)
5	DEP - SUB	1.9 (157)	HTN - DEP	2.4 (203)	LIP - DEP - DIA	0.8 (74)	LIP - DEP - AST	0.6 (63)
50 – 59								
1	LIP - HTN	14.5 (757)	LIP - HTN	9.8 (540)	LIP - HTN - DIA	7.2 (504)	LIP - HTN - DIA	3.9 (300)
2	LIP - DIA	8.7 (455)	LIP - ART	6.5 (359)	LIP - HTN - ART	3.5 (242)	LIP - HTN - ART	3.0 (232)
3	LIP - ART	6.7 (351)	LIP - DEP	5.9 (325)	LIP - HTN - CAD	3.0 (208)	LIP - HTN - DEP	2.4 (185)
4	LIP - CAN	4.6 (241)	DEP - ART	4.8 (265)	LIP - HTN - DEP	1.9 (131)	LIP - DEP - ART	2.4 (180)
5	HTN - DIA	4.4 (227)	LIP - CAN	4.5 (246)	LIP - HTN - ARR	1.7 (117)	LIP - HTN - CAN	1.8 (136)

Table 3. Continued 1

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
60 – 69								
1	LIP - HTN	23.4 (460)	LIP - HTN	18.8 (400)	LIP - HTN - DIA	11.6 (366)	LIP - HTN - ART	10.3 (363)
2	LIP - DIA	11.5 (226)	LIP - ART	15.5 (330)	LIP - HTN - ART	6.8 (214)	LIP - HTN - DIA	7.4 (263)
3	LIP - ART	11.4 (224)	HTN - ART	10.4 (220)	LIP - HTN - CAD	6.3 (200)	LIP - HTN - CAN	4.6 (164)
4	LIP - CAN	10.0 (196)	LIP - CAN	6.8 (145)	LIP - HTN - CAN	4.9 (155)	LIP - ART - CAN	2.9 (102)
5	HTN - DIA	8.6 (169)	LIP - DIA	6.4 (135)	LIP - HTN - ARR	3.4 (106)	LIP - DIA - ART	2.7 (95)
6	HTN - ART	7.7 (152)	ART - CAN	4.9 (105)	LIP - DIA - ART	2.9 (91)	LIP - HTN - DEP	2.6 (93)
7	LIP - CAD	6.9 (136)	LIP - OST	4.9 (105)	LIP - ART - CAN	2.6 (82)	LIP - DEP - ART	2.5 (89)
8	HTN - CAN	6.2 (121)	HTN - CAN	4.8 (103)	LIP - DIA - CAD	2.4 (76)	LIP - ART - ARR	2.3 (83)
9	ART - CAN	4.5 (89)	HTN - DIA	4.6 (97)	HTN - DIA - ART	2.2 (71)	LIP - HTN - OST	2.2 (79)
10	LIP - ARR	4.5 (88)	LIP - DEP	4.4 (94)	LIP - ARR - CAD	2.2 (68)	HTN - DIA - ART	2.2 (77)
70 – 79								
1	LIP - HTN	19.1 (104)	LIP - HTN	26.0 (173)	LIP - HTN - CAN	11.9 (127)	LIP - HTN - ART	15.7 (214)
2	HTN - CAN	18.9 (103)	HTN - ART	18.5 (123)	LIP - HTN - DIA	10.4 (111)	LIP - HTN - DIA	9.8 (134)
3	LIP - CAN	15.0 (82)	LIP - ART	15.5 (103)	LIP - HTN - CAD	9.7 (103)	LIP - HTN - CAN	6.0 (82)
4	HTN - ART	13.2 (72)	LIP - OST	9.0 (60)	LIP - HTN - ART	9.4 (100)	LIP - ART - CAN	5.4 (74)
5	ART - CAN	11.6 (63)	HTN - CAN	8.9 (59)	LIP - HTN - ARR	5.5 (58)	HTN - ART - CAN	5.2 (71)
6	LIP - ART	11.6 (63)	HTN - OST	8.3 (55)	HTN - ART - CAN	4.9 (52)	LIP - ART - OST	5.2 (71)
7	HTN - DIA	10.1 (55)	ART - CAN	8.1 (54)	LIP - ART - CAN	4.7 (50)	LIP - HTN - OST	4.6 (63)
8	HTN - ARR	9.9 (54)	ART - OST	7.8 (52)	HTN - CAN - ARR	4.2 (45)	LIP - HTN - ARR	4.5 (62)
9	LIP - CAD	7.7 (42)	HTN - DIA	7.8 (52)	HTN - ART - ARR	4.1 (44)	HTN - ART - OST	4.0 (55)
10	LIP - DIA	7.7 (42)	LIP - CAN	7.8 (52)	LIP - DIA - CAN	4.1 (44)	2-way tie ¶	3.4 (47)
≥ 80								
1	HTN - CAN	18.9 (30)	HTN - ART	27.7 (80)	HTN - CAN - ARR	8.7 (28)	LIP - HTN - ART	10.3 (66)
2	HTN - ARR	17.6 (28)	LIP - HTN	23.2 (67)	LIP - HTN - CAN	7.7 (25)	HTN - ART - OST	9.8 (63)
3	HTN - ART	14.5 (23)	HTN - ARR	17.7 (51)	HTN - ART - CAN	7.4 (24)	HTN - ART - CAN	9.2 (59)

Table 3. Continued 2

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
4	ART - ARR	12.0 (19)	HTN - CAN	15.2 (44)	LIP - HTN - ART	6.2 (20)	HTN - ART - ARR	9.0 (58)
5	CAN - ARR	12.0 (19)	HTN - OST	14.9 (43)	LIP - HTN - ARR	5.9 (19)	LIP - HTN - OST	5.9 (38)
6	HTN - CAD	10.1 (16)	HTN - DEM	11.8 (34)	ART - CAN - ARR	5.3 (17)	LIP - HTN - DIA	5.0 (32)
7	LIP - HTN	10.1 (16)	ART - CAN	10.0 (29)	HTN - ART - ARR	5.3 (17)	LIP - HTN - ARR	4.7 (30)
8	ART - CAN	8.8 (14)	ART - OST	9.7 (28)	HTN - CAN - CAD	5.0 (16)	LIP - HTN - CAN	4.5 (29)
9	CAN - CAD	8.8 (14)	HTN - CKD	7.6 (22)	LIP - HTN - CAD	5.0 (16)	ART - CAN - OST	4.4 (28)
10	HTN - DEM	8.8 (14)	3-way tie **	7.3 (21)	LIP - ART - CAN	4.6 (15)	LIP - HTN - CAD	3.9 (25)

* Rank order from the most frequent to the least frequent incident dyad or triad. For the younger age groups (through age 59 years), we reported the 5 most frequent incident combinations; for the older age groups (60 years and older), we reported the 10 most frequent incident combinations.

† Definition of acronyms in order of frequency: LIP = hyperlipidemia; HTN = hypertension; DEP = depression; DIA = diabetes; ART = arthritis; CAN = cancer; ARR = cardiac arrhythmias; AST = asthma; CAD = coronary artery disease; SUB = substance abuse disorders; COPD = chronic obstructive pulmonary disease; OST = osteoporosis; CKD = chronic kidney disease; STR = stroke; CHF = congestive heart failure; DEM = dementia; SZO = schizophrenia; HEP = hepatitis; AUT = autism spectrum disorder; and HIV = human immunodeficiency virus.

‡ Incidence rates per 1,000 person years. Rates can be calculated by dividing the number of incident persons in parentheses by the person- years at risk of 2 conditions from each age- and sex-specific stratum for all ethnic groups combined in Table 1.

§ Incidence rates per 1,000 person years. Rates can be calculated by dividing the number of incident persons in parentheses by the person-years at risk of 3 conditions from each age- and sex-specific stratum for all ethnic groups combined in Table 2.

‖ Three-way tie for the rank 5 triad in men ages 0-19 years: 1) AST-SUB-COPD; 2) DEP-ARR-SUB; 3) DEP-AST-DEM.

¶ Two-way tie for the rank 10 triad in women ages 70-79 years: 1) HTN-ART-ARR; 2) LIP-CAN-OST.

** Three-way tie for the rank 10 dyad in women ages ≥ 80 years: 1) ART-ARR; 2) HTN-DIA; 3) LIP-ART.

Figure Legends

Figure 1. Age- and sex-specific incidence rates (per 1,000 person-years) of the 20 chronic conditions considered separately. The 20 panels are presented by rows in decreasing order of frequency (by overall age- and sex-standardized prevalence). [16]

Figure 2. Incidence rates (per 1,000 person-years) of 2 chronic conditions (second condition in a dyad) and of 3 chronic conditions (third condition in a triad) in men and women separately (panels A and C), and stratified by ethnicity (panels B and D).

Figure 1

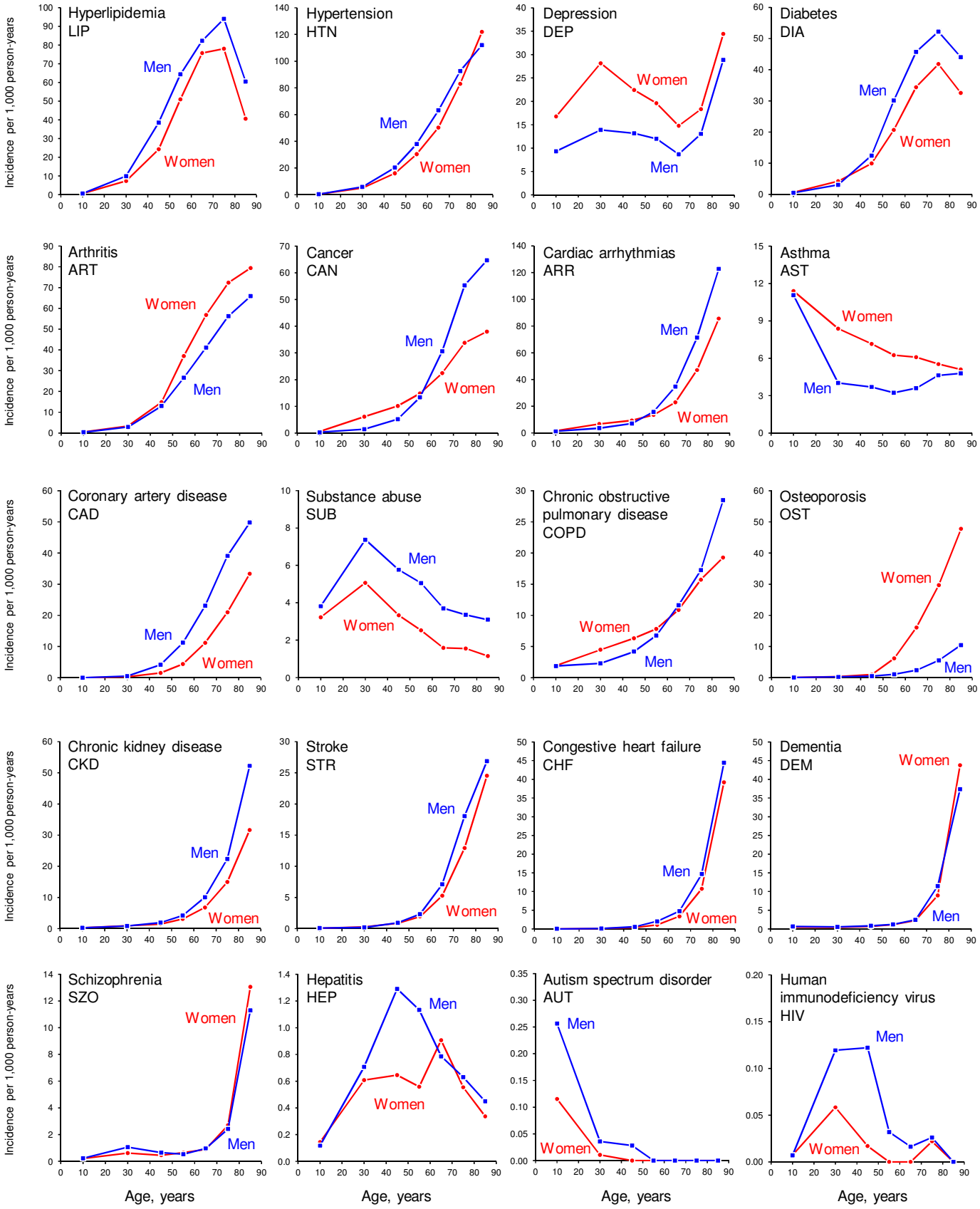
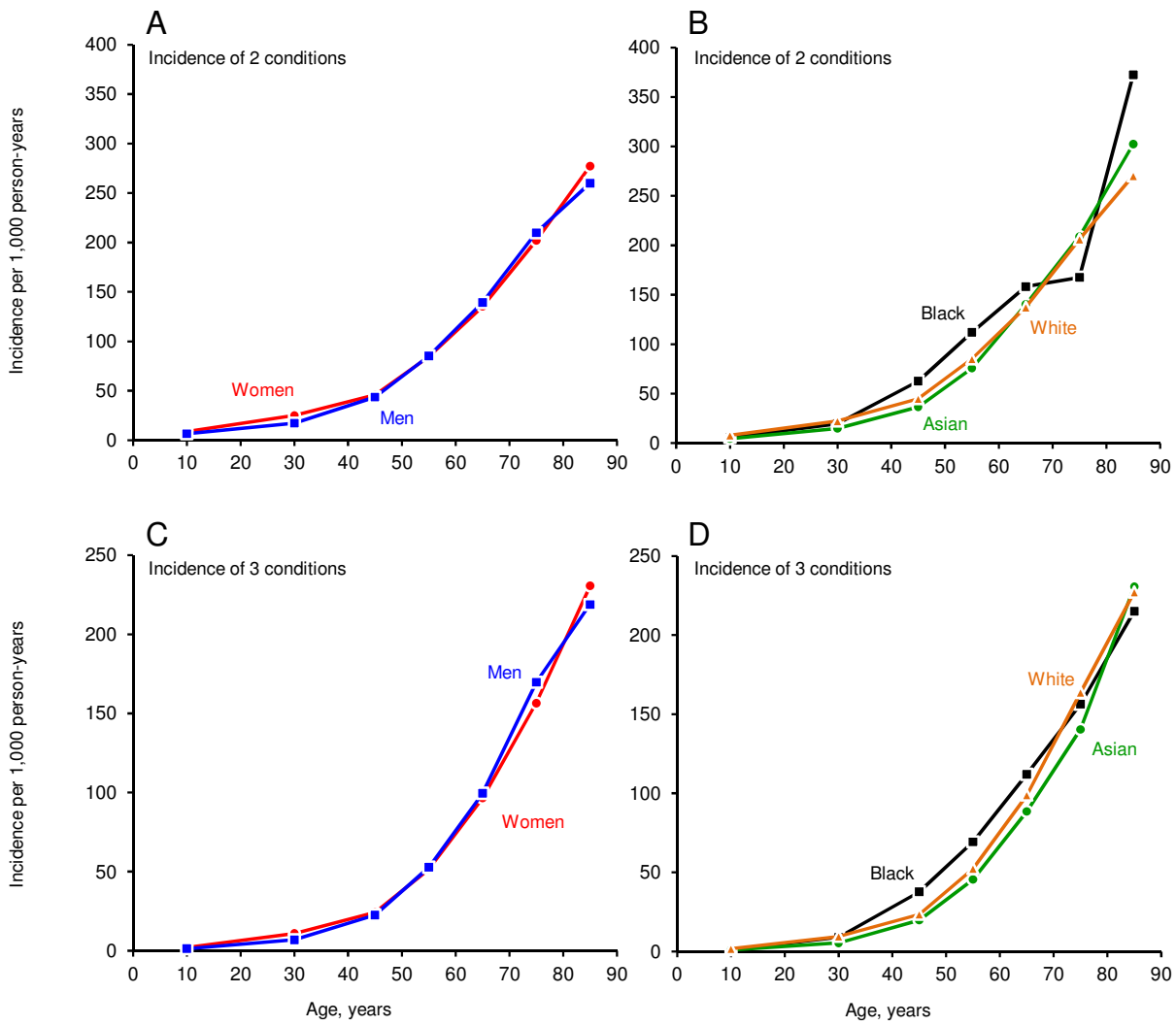

Hyperlipidemia
LIP
Men
Women
Hypertension
HTN
Men
Women
Depression
DEP
Women
Men
Diabetes
DIA
Men
Women
Arthritis
ART
Women
Men
Cancer
CAN
Men
Women
Cardiac arrhythmias
ARR
Men
Women
Asthma
AST
Women
Men
Coronary artery disease
CAD
Men
Women
Substance abuse
SUB
Men
Women
Chronic obstructive pulmonary disease
COPD
Women
Men
Osteoporosis
OST
Women
Men
Chronic kidney disease
CKD
Men
Women
Stroke
STR
Men
Women
Congestive heart failure
CHF
Men
Women
Dementia
DEM
Women
Men
Schizophrenia
SZO
Women
Men
Hepatitis
HEP
Men
Women
Autism spectrum disorder
AUT
Men
Women
Human immunodeficiency virus
HIV
Men
Women
Incidence per 1,000 person-years
Age, years

Figure 2



Appendix 1: Supplementary tables A-C [posted as supplied by the authors]

Supplementary table A. List of the twenty chronic conditions selected by the US-DHHS *

Description †	Acronym or Abbreviation	CCC ‡	CMS (ICD-9 codes) §
Hyperlipidemia	LIP	53	272.0, 272.1, 272.2, 272.3, 272.4
Hypertension	HTN	98, 99	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 362.11, 437.2
Depression	DEP	657	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	DIA	49,50	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
Arthritis	ART	202, 203	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91
Cancer	CAN	11-43	Female breast cancer: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3. Colorectal cancer: 154.0, 154.1, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 230.3, 230.4, V10.05. Prostate cancer: 185, 233.4, V10.46. Lung cancer: 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11.
Cardiac arrhythmias	ARR	105-106	427.31
Asthma	AST	128	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Coronary artery disease	CAD	100, 101	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.8, 414.9

Supplementary table A. List of the twenty chronic conditions selected by the US-DHHS * (continued)

Description †	Acronym or Abbreviation	CCC ‡	CMS (ICD-9 codes) §
Substance abuse disorders (drug and alcohol)	SUB	660-661	Not applicable
Chronic obstructive pulmonary disease	COPD	127	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496
Osteoporosis	OST	206	733.00, 733.01, 733.02, 733.03, 733.09
Chronic kidney disease	CKD	158	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Stroke	STR	109-112	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01,434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Congestive heart failure	CHF	108	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Dementia (including Alzheimer's and other senile dementias)	DEM	653	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.8, 797
Schizophrenia	SZO	659	Not applicable
Hepatitis	HEP	6	Not applicable
Autism spectrum disorder	AUT	299.00, 299.01 ‖	Not applicable
Human immunodeficiency virus (HIV)	HIV	5	Not applicable

* CCC = Clinical Classification Codes; CMS = Centers for Medicare and Medicaid Services; ICD-9 = International Classification of Diseases, 9th revision; US-DHHS = US Department of Health and Human Services.

† The 20 conditions were defined by the US-DHHS as detailed elsewhere. (Goodman et al., 2013) Each condition is defined by having a code in either the CCC group of codes or the CMS group of codes. Conditions are listed in decreasing order of frequency (by overall age and sex standardized prevalence; same order as in Figure 1).

‡ We list the CCC chapters developed by the Agency for Healthcare Research and Quality (AHRQ). Each CCC chapter includes a list of ICD-9 codes as detailed elsewhere. (Cohen et al., 2009)

§ We list the ICD-9 codes defined in the Chronic Conditions Data Warehouse of the CMS.

‖ Autism-spectrum disorder is not defined in either the CCC or the CMS code groupings, but rather is defined by two distinct ICD-9 codes.

Supplementary table B. Total US population used for direct standardization of incidence rates

Age	Men			Women			Adjusting population §
	US Total (n) *	Prev. % †	At risk (n) ‡	US Total (n) *	Prev. % †	At risk (n) ‡	
Prevalence of 2 chronic conditions							
0-19 y	42,592	1.26	42,054	40,675	1.40	40,108	82,162
20-39 y	41,688	6.98	38,779	41,140	8.74	37,546	76,325
40-49 y	21,603	20.37	17,202	21,995	19.71	17,660	34,862
50-59 y	20,456	38.13	12,657	21,505	35.77	13,813	26,470
60-69 y	13,930	59.41	5,654	15,323	58.35	6,381	12,036
70-79 y	7,427	79.73	1,506	9,170	78.27	1,993	3,498
≥ 80 y	4,084	87.86	496	7,152	86.41	972	1,467
Prevalence of 3 chronic conditions							
0-19 y	42,592	0.17	42,521	40,675	0.25	40,575	83,096
20-39 y	41,688	2.12	40,805	41,140	2.57	40,083	80,887
40-49 y	21,603	9.40	19,572	21,995	8.55	20,115	39,687
50-59 y	20,456	21.06	16,148	21,505	19.30	17,355	33,503
60-69 y	13,930	40.88	8,235	15,323	38.32	9,452	17,687
70-79 y	7,427	65.11	2,591	9,170	62.05	3,480	6,071
≥ 80 y	4,084	78.93	861	7,152	74.17	1,848	2,708

* Population (in thousands) of the entire United States from the decennial census of 2010.
† Prevalence of 2 or 3 chronic conditions from our previous study in Olmsted County, MN. (Rocca et., al, In Press)
‡ Total population at risk (in thousands) after removing the estimated prevalent persons who have already reached 2 or 3 chronic conditions.
§ The total population (in thousands) used in Tables 1 and 2 for direct standardization.

Supplementary table C. Incidence of twenty chronic conditions considered individually

Condition age (years)	Men Persons	Men Person-years	Men Incidence rate * (n)	Women Persons	Women Person-years	Women Incidence rate * (n)
Hyperlipidemia						
0-19	18,996	143,882	0.6 (91)	18,174	138,140	0.7 (94)
20-39	28,437	159,373	10.0 (1,586)	30,040	179,745	7.3 (1,311)
40-49	16,512	82,705	38.5 (3,186)	18,328	99,834	24.3 (2,428)
50-59	11,993	54,436	64.4 (3,504)	14,248	68,637	51.0 (3,500)
60-69	6,023	25,216	82.4 (2,077)	7,111	30,967	75.7 (2,345)
70-79	3,077	11,661	94.1 (1,097)	3,821	14,970	78.0 (1,168)
≥ 80	1,712	7,163	60.5 (433)	3,319	15,777	40.6 (641)
Hypertension						
0-19	19,029	144,237	0.5 (65)	18,215	138,569	0.4 (51)
20-39	28,626	162,582	5.9 (954)	30,315	183,220	5.0 (908)
40-49	17,289	92,372	20.4 (1,882)	18,790	105,079	16.0 (1,683)
50-59	13,481	67,250	38.0 (2,556)	15,013	77,172	30.3 (2,341)
60-69	7,077	31,540	63.2 (1,993)	7,971	36,990	50.3 (1,859)
70-79	3,331	13,402	92.6 (1,241)	3,941	16,136	83.0 (1,339)
≥ 80	1,354	5,198	112.0 (582)	2,053	7,919	121.9 (965)
Depression						
0-19	18,794	139,315	9.3 (1,297)	17,774	131,126	16.8 (2,198)
20-39	27,342	150,493	13.9 (2,091)	27,026	146,257	28.2 (4,118)
40-49	17,234	94,033	13.2 (1,238)	16,533	89,742	22.4 (2,013)
50-59	15,027	81,059	12.0 (974)	14,642	77,962	19.6 (1,530)
60-69	10,174	54,355	8.7 (472)	10,229	54,471	14.8 (805)
70-79	6,720	34,274	13.0 (447)	7,408	37,536	18.3 (688)
≥ 80	3,482	17,009	28.9 (491)	5,313	28,290	34.4 (974)
Diabetes						
0-19	19,025	144,155	0.5 (68)	18,190	138,186	0.7 (90)
20-39	28,799	165,115	3.0 (503)	30,406	184,616	4.2 (775)
40-49	18,193	100,104	12.4 (1,246)	19,617	112,231	9.9 (1,112)
50-59	15,419	80,259	30.1 (2,417)	17,181	92,695	20.7 (1,917)
60-69	9,394	45,589	45.7 (2,084)	10,854	55,408	34.4 (1,906)
70-79	5,427	25,396	52.2 (1,326)	6,966	33,383	41.8 (1,395)
≥ 80	2,840	13,550	44.1 (597)	5,074	26,909	32.6 (876)
Arthritis						
0-19	19,032	144,320	0.3 (49)	18,205	138,450	0.5 (68)
20-39	28,827	165,354	2.9 (477)	30,425	185,391	3.4 (625)
40-49	18,202	99,821	13.0 (1,298)	19,464	109,658	14.8 (1,628)
50-59	15,324	79,753	26.6 (2,120)	16,304	83,158	37.0 (3,079)
60-69	9,295	45,576	41.1 (1,874)	9,227	43,244	56.8 (2,458)
70-79	5,193	23,106	56.3 (1,300)	5,185	22,090	72.3 (1,598)
≥ 80	2,317	9,836	65.9 (648)	3,252	14,434	79.4 (1,146)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 1)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Cancer						
0-19	19,020	144,181	0.3 (40)	18,180	138,347	0.6 (84)
20-39	28,832	166,077	1.5 (241)	29,734	176,247	6.1 (1,079)
40-49	18,402	103,035	5.2 (534)	18,658	105,898	10.1 (1,072)
50-59	15,899	85,763	13.4 (1,145)	16,361	89,149	14.8 (1,321)
60-69	9,821	49,157	30.7 (1,507)	10,480	54,117	22.5 (1,215)
70-79	5,146	23,169	55.3 (1,281)	6,552	31,563	33.7 (1,065)
≥ 80	2,112	9,137	64.7 (591)	4,411	21,933	38.0 (833)
Cardiac arrhythmias						
0-19	19,008	143,802	1.2 (170)	18,203	137,966	1.7 (228)
20-39	28,736	164,530	3.6 (590)	30,250	181,665	6.7 (1,216)
40-49	18,324	102,268	7.1 (722)	19,444	110,842	9.3 (1,036)
50-59	15,939	85,675	15.8 (1,354)	17,211	94,404	13.5 (1,274)
60-69	10,068	50,190	34.7 (1,741)	11,262	58,346	22.9 (1,337)
70-79	5,514	24,370	71.4 (1,741)	7,095	33,211	47.1 (1,563)
≥ 80	2,193	8,604	122.9 (1,057)	4,365	20,213	85.6 (1,731)
Asthma						
0-19	17,856	126,216	11.1 (1,395)	17,443	125,314	11.4 (1,428)
20-39	27,126	155,022	4.0 (624)	28,383	168,182	8.4 (1,409)
40-49	18,102	101,654	3.7 (376)	18,845	107,595	7.2 (770)
50-59	16,129	89,329	3.2 (289)	16,920	94,186	6.3 (589)
60-69	10,930	58,658	3.6 (211)	11,535	62,226	6.1 (379)
70-79	7,051	36,059	4.6 (167)	7,987	41,216	5.5 (228)
≥ 80	3,741	18,815	4.8 (90)	5,878	32,584	5.1 (166)
Coronary artery disease						
0-19	19,050	144,593	0.0 (0)	18,227	138,785	0.0 (0)
20-39	28,982	167,484	0.5 (79)	30,647	188,499	0.3 (50)
40-49	18,565	104,424	4.1 (432)	20,213	117,920	1.5 (177)
50-59	15,875	85,866	11.2 (963)	18,177	101,860	4.4 (446)
60-69	9,540	47,996	23.1 (1,108)	11,891	62,970	11.2 (703)
70-79	5,081	23,713	39.1 (927)	7,473	37,099	21.0 (779)
≥ 80	2,213	10,046	49.8 (500)	4,868	25,325	33.4 (845)
Substance abuse disorders						
0-19	18,850	142,916	3.8 (545)	18,083	137,309	3.2 (443)
20-39	28,004	157,109	7.4 (1,159)	29,846	179,474	5.1 (910)
40-49	18,038	100,943	5.8 (582)	19,722	114,415	3.3 (381)
50-59	16,085	89,151	5.1 (451)	18,013	101,745	2.5 (257)
60-69	11,001	59,373	3.7 (220)	12,398	67,817	1.6 (108)
70-79	7,194	37,259	3.4 (125)	8,599	44,899	1.6 (70)
≥ 80	3,882	19,697	3.1 (61)	6,325	35,542	1.2 (41)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 2)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Chronic obstructive pulmonary disease						
0-19	18,973	142,682	1.9 (267)	18,140	136,992	1.9 (263)
20-39	28,674	164,415	2.3 (376)	30,052	181,106	4.5 (811)
40-49	18,348	103,031	4.2 (430)	19,432	111,533	6.3 (704)
50-59	16,170	88,965	6.7 (600)	17,425	96,719	7.8 (756)
60-69	10,615	55,796	11.6 (648)	11,556	61,640	10.9 (670)
70-79	6,439	32,418	17.2 (559)	7,661	38,688	15.7 (608)
≥ 80	3,234	15,771	28.5 (449)	5,397	29,472	19.3 (568)
Osteoporosis						
0-19	19,048	144,579	<0.1 (5)	18,226	138,759	<0.1 (5)
20-39	28,982	167,571	0.2 (41)	30,631	188,380	0.3 (58)
40-49	18,740	106,337	0.5 (53)	20,191	117,986	1.0 (119)
50-59	16,745	93,377	1.1 (99)	18,194	101,448	6.2 (628)
60-69	11,326	60,849	2.4 (144)	11,750	61,299	16.1 (987)
70-79	7,280	37,236	5.5 (206)	7,330	34,844	29.7 (1,034)
≥ 80	3,825	18,929	10.5 (198)	4,818	23,172	47.8 (1,107)
Chronic kidney disease						
0-19	19,007	143,995	0.3 (37)	18,200	138,410	0.2 (33)
20-39	28,896	166,662	0.8 (138)	30,555	187,402	0.9 (173)
40-49	18,626	105,218	1.9 (200)	20,119	117,418	1.4 (170)
50-59	16,546	91,726	4.2 (386)	18,264	102,861	3.1 (317)
60-69	11,049	58,474	10.1 (589)	12,300	66,388	6.8 (452)
70-79	6,896	34,352	22.4 (768)	8,330	42,336	15.0 (634)
≥ 80	3,462	16,119	52.2 (842)	5,916	31,586	31.6 (999)
Stroke						
0-19	19,044	144,494	0.1 (11)	18,225	138,714	0.1 (10)
20-39	28,966	167,513	0.2 (32)	30,625	188,279	0.3 (54)
40-49	18,723	106,112	0.9 (98)	20,195	118,033	0.9 (101)
50-59	16,663	92,757	2.3 (215)	18,316	103,296	1.9 (200)
60-69	11,095	58,984	7.1 (420)	12,326	66,626	5.3 (352)
70-79	6,787	33,726	18.1 (609)	8,155	41,474	12.9 (536)
≥ 80	3,302	16,079	26.9 (432)	5,578	29,934	24.5 (734)
Congestive heart failure						
0-19	19,049	144,577	<0.1 (3)	18,225	138,741	<0.1 (1)
20-39	28,991	167,636	0.1 (23)	30,643	188,550	0.1 (27)
40-49	18,748	106,429	0.6 (60)	20,247	118,489	0.4 (44)
50-59	16,715	93,129	2.0 (189)	18,420	104,263	1.1 (113)
60-69	11,200	60,021	4.7 (284)	12,468	67,862	3.4 (228)
70-79	7,023	35,739	14.7 (524)	8,373	43,018	10.7 (462)
≥ 80	3,454	16,474	44.4 (732)	5,644	30,042	39.2 (1,178)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 3)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Dementia						
0-19	19,045	144,233	0.7 (95)	18,224	138,612	0.5 (65)
20-39	28,927	167,098	0.5 (90)	30,613	188,229	0.4 (74)
40-49	18,730	106,234	0.8 (87)	20,234	118,263	0.7 (80)
50-59	16,732	93,398	1.2 (113)	18,391	104,060	1.2 (122)
60-69	11,339	61,016	2.4 (147)	12,527	68,389	2.2 (152)
70-79	7,250	37,024	11.5 (424)	8,523	44,015	9.0 (394)
≥ 80	3,651	17,816	37.4 (666)	5,684	30,237	43.8 (1,324)
Schizophrenia						
0-19	19,043	144,539	0.2 (32)	18,221	138,684	0.2 (28)
20-39	28,905	166,386	1.1 (177)	30,559	187,680	0.6 (116)
40-49	18,656	105,803	0.6 (68)	20,132	117,772	0.5 (53)
50-59	16,695	93,305	0.5 (49)	18,333	103,725	0.6 (67)
60-69	11,357	61,286	1.0 (59)	12,474	68,212	0.9 (61)
70-79	7,338	38,011	2.4 (92)	8,586	44,755	2.7 (121)
≥ 80	3,892	19,550	11.3 (221)	6,114	34,000	13.1 (444)
Hepatitis						
0-19	19,041	144,470	0.1 (17)	18,216	138,646	0.1 (20)
20-39	28,927	166,978	0.7 (118)	30,557	187,564	0.6 (114)
40-49	18,620	105,303	1.3 (136)	20,126	117,719	0.6 (76)
50-59	16,599	92,627	1.1 (105)	18,340	103,834	0.6 (58)
60-69	11,293	61,018	0.8 (48)	12,506	68,411	0.9 (62)
70-79	7,353	38,053	0.6 (24)	8,634	45,080	0.6 (25)
≥ 80	3,936	20,045	0.4 (9)	6,350	35,622	0.3 (12)
Autism spectrum disorder						
0-19	19,031	144,197	0.3 (37)	18,224	138,664	0.1 (16)
20-39	28,972	167,636	<0.1 (6)	30,643	188,651	<0.1 (2)
40-49	18,778	106,682	<0.1 (3)	20,275	118,760	0.0 (0)
50-59	16,810	94,079	0.0 (0)	18,480	104,783	0.0 (0)
60-69	11,424	61,702	0.0 (0)	12,603	69,065	0.0 (0)
70-79	7,409	38,416	0.0 (0)	8,704	45,493	0.0 (0)
≥ 80	3,966	20,174	0.0 (0)	6,383	35,849	0.0 (0)
Human immunodeficiency virus						
0-19	19,049	144,591	<0.1 (1)	18,227	138,772	<0.1 (1)
20-39	28,985	167,674	0.1 (20)	30,646	188,628	0.1 (11)
40-49	18,756	106,511	0.1 (13)	20,265	118,694	<0.1 (2)
50-59	16,794	94,006	<0.1 (3)	18,476	104,777	0.0 (0)
60-69	11,420	61,680	<0.1 (1)	12,603	69,065	0.0 (0)
70-79	7,408	38,407	<0.1 (1)	8,704	45,489	<0.1 (1)
≥ 80	3,964	20,171	0.0 (0)	6,383	35,849	0.0 (0)

* Incidence rates are reported per 1,000 person-years, and are calculated by dividing the number of observed new cases in parentheses by the number of observed person-years of risk within each age and sex stratum. The 20 chronic conditions are listed in decreasing order of frequency (by overall age- and sex-standardized prevalence). (Rocca et., al, 2013)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	14-17
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9, 16
		(*e*) Describe any sensitivity analyses	10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13, Tables 1-3, Figures 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Tables 1-3, Figures 1 and 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity

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Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity

Jennifer L. St. Sauver *associate professor* [1 2], Cynthia M. Boyd *associate professor* [3], Brandon R. Grossardt *biostatistician* [4], William V. Bobo *assistant professor* [5], Lila J. Finney Rutten *associate professor* [1 2], Véronique L. Roger *professor* [1 2 6], Jon O. Ebbert *professor* [2], Terry M. Therneau *professor* [4], Barbara P. Yawn *director of research* [1 7], Walter A. Rocca *professor* [1 8]

Author Affiliations: [1] Division of Epidemiology, Department of Health Sciences Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [2] The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [3] Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287, USA; [4] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [5] Department of Psychiatry and Psychology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [6] Division of Cardiovascular Diseases, Department of Internal Medicine, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [7] Department of Research, Olmsted Medical Center, 210 Ninth Street SE, Rochester, MN 55904, USA; [8] Department of Neurology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

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Figures/Tables: (5/5)

Supplementary Tables: 3

Corresponding Author: Walter A. Rocca, MD, MPH, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (telephone: 507-284-3568; fax: 507-284-1516; e-mail: rocca@mayo.edu).

Extra material supplied by the author: Supplementary tables A-C

ABSTRACT

Objective: To study the incidence of de novo multimorbidity across all ages in a geographically defined population with an emphasis on sex and ethnic differences.

Design: Historical cohort study.

Setting: All persons residing in Olmsted County, Minnesota, USA on January 1, 2000 who had not refused permission for their records to be used for research (n = 123,716).

Participants: We used the Rochester Epidemiology Project medical records-linkage system to identify all of the county residents. We identified and removed from the cohort all persons who had developed multimorbidity before January 1, 2000 (baseline date), and we followed the cohort over 14 years (January 1, 2000 through December 31, 2013).

Main outcome measures: Incident multimorbidity was defined as the development of the second of 2 conditions (dyads) from among the 20 chronic conditions selected by the United States Department of Health and Human Services. We also studied the incidence of the third of 3 conditions (triads) from among the 20 chronic conditions.

Results: The incidence of multimorbidity increased steeply with older age; however, the number of people with incident multimorbidity was substantially greater in people younger than 65 years compared to people age 65 years or older (28,378 vs. 6,214).

The overall risk was similar in men and women; however, the combinations of conditions (dyads and triads) differed extensively by age and by sex. Compared to Whites, the incidence of multimorbidity was higher in Blacks and lower in Asians.

Conclusions: The risk of developing de novo multimorbidity increases steeply with older age, varies by ethnicity, and is similar in men and women overall. However, as expected, the combinations of conditions vary extensively by age and sex. These data represent an important first step toward identifying the causes and the consequences of multimorbidity.

ARTICLE SUMMARY: Strengths and limitations of this study

- This is one of the first studies worldwide focusing on the incidence of multimorbidity rather than on the prevalence of multimorbidity. Prevalence reflects both the effect of incidence and of survival after the onset of multimorbidity. We used a simple definition of incident multimorbidity that can be replicated in other populations.
- This study covered an entire geographically defined population, and used a unique records-linkage system. Persons were followed historically over 14 years. None of the data were derived from self-report or interviews.
- Studies of multimorbidity require the definition of the number of conditions considered, of the time window of occurrence, and of the source of data (medical records vs. interview). We used the 20 conditions recommended by the United States Department of Health and Human Services. These 20 conditions represent a first consensus list; however, not all of the conditions have the same impact on the complexity of care or on the quality of life of patients.
- Potential limitations of this study include the uncertain validity of diagnostic codes, the possible incompleteness of information due to in or out migration, and the inability to generalize our findings to other populations with different demographic or social characteristics.
- Replication of this study in other populations in the United States and worldwide will allow for useful comparisons.

INTRODUCTION

The demographic expansion of the elderly population and the improvements in survival of people affected by chronic conditions have caused a dramatic rise in the number of people living with multimorbidity (≥ 2 chronic conditions). In the United States, the prevalence of multimorbidity among Medicare recipients increases from 62% at age 65 - 74 years to 82% at ages 85 years and older. [1] The monetary costs associated with managing patients with multiple chronic conditions are overwhelming. [2-4] In addition, fragmented health care in patients with multimorbidity causes a particularly high risk for complications and a lower quality of life. [5,6]

Several studies have described the prevalence of multimorbidity in a wide range of populations. [1,7-12] Additional studies have focused on how to manage patients with multiple chronic conditions. [13,14] However, in 2010 the United States Department of Health and Human Services (US-DHHS) highlighted the critical need to identify groups of individuals at higher risk of developing multimorbidity (first appearance of multimorbidity). Such studies of incident multimorbidity are essential to identify patterns of disease accumulation, and to identify the populations at high risk of developing multimorbidity. For example, multimorbidity is highly prevalent in the elderly; however, many of the processes that lead to multimorbidity begin at much earlier ages. Therefore, data on the ages at which multimorbidity begins and on the patterns of accumulation of conditions over time are urgently needed to develop focused interventions to prevent multimorbidities and their adverse health outcomes. [15]

Unfortunately, there are currently no population-based data on the incidence of multimorbidity in the United States across all ages, even though multimorbidity is a high

public health priority for the nation. [15] The Rochester Epidemiology Project (REP) medical records-linkage system captures long-term medical information on a stable population, and is therefore uniquely positioned to study the incidence of multimorbidity. In a previous paper, we described in detail the patterns of prevalent multimorbidity in this population. [16] In this study, we further leveraged this data resource to examine the incidence of multimorbidity across all ages, separately in men and women, and in three ethnic groups. [17]

METHODS

Study population

The REP has tracked and linked health care information for the population of Olmsted County, MN, since 1966.[17-19] The vast majority of medical care in this community is currently provided by a few health care institutions: Olmsted Medical Center and its affiliated hospital, Mayo Clinic and its two affiliated hospitals, the Rochester Family Medicine Clinic, and a few smaller care facilities. The health care records from these institutions are linked together through the REP records-linkage system. [17-19] Persons are considered residents of Olmsted County at the time of each health care visit based on their address. Over the years, this address information has been accumulated and is used to define who resided in Olmsted County at any given point in time since 1966 (REP Census). The population counts obtained by the REP Census are similar to those obtained by the US Census, indicating that virtually the entire population of the county is captured by the system. [18-20] We used the REP Census to identify all individuals who resided in Olmsted County on January 1, 2000 (baseline date); however, we included

only individuals who had not refused permission to use their medical records for research (Minnesota research authorization). [18,21,22]

Definition of incident multimorbidity

We focused on 20 selected chronic conditions recommended by the US-DHHS for studying multimorbidity. [23,24] The list of the 20 conditions and the corresponding ICD-9 codes used in this study are provided in Supplementary Table A. [23,24] We first identified all ICD-9 codes associated with these 20 chronic conditions that occurred in the population between January 1, 1995 and December 31, 1999 (5 years before the baseline date, January 1, 2000). Persons who did not have any ICD-9 code for a given condition were assumed to not have the condition of interest. By contrast, residents were defined as having a chronic condition if they had at least two ICD-9 codes for that condition separated by more than 30 days, and the incidence date was assigned at the time they received a second diagnostic code.

Persons who had 2 or more of the 20 conditions at baseline were considered to have prevalent multimorbidity and were therefore excluded from incidence analyses of 2 chronic conditions (dyads). Similarly, persons who had 3 or more of the 20 conditions at baseline were excluded from incidence analyses of 3 chronic conditions (triads). All persons in this fixed population cohort were followed historically through the REP records-linkage system for approximately 14 years to study the emergence of new conditions.

Statistical Analyses

All persons in the cohort were followed from January 1, 2000 through the last contact with the records-linkage system (the earliest of death date, last medical visit date, or December 31, 2013). The incidence of each of the 20 chronic conditions was calculated among persons free of that condition at baseline. Persons contributed person-years to the denominator for the incidence of 2 conditions (development of a second condition in a dyad) only during the time when they had 0 or 1 chronic conditions, whereas persons contributed person-years to the denominator for the incidence of 3 chronic conditions (development of a third condition in a triad) only when they had 0, 1, or 2 chronic conditions. Although the majority of people accumulated conditions one-at-a-time, some subjects jumped from 0 to 2 conditions, or from 1 to 3, or even from 0 to 3 conditions. For example, a person previously considered free of all of the 20 conditions who was diagnosed with hyperlipidemia, hypertension, and depression during one visit was counted as having three incident dyads and one incident triad on the same date.

Incidence rates were reported separately by age (using seven age strata or splitting the entire population in 0-64 and ≥ 65 years), sex, and ethnicity, and were directly standardized by age and sex to the total US 2010 Decennial Census after removing projected prevalence (see Supplementary Table B). Because the study covered the target population completely, and no sampling was involved, confidence intervals were not included in the tables. [25,26] Ethnicity data were not available for 9,176 people (7.4% of the cohort). These individuals were included in the overall and age- and sex-specific analyses, but not in the ethnicity-specific analyses.

Although the 20 conditions proposed by the US-DHHS represent a national consensus, [15] some of the conditions may have a different prognostic impact than others. For example, hyperlipidemia and hypertension often occur together and tend to remain asymptomatic. Therefore, we performed a set of sensitivity analyses combining hyperlipidemia and hypertension as a single chronic condition. The date of incidence for the single chronic condition of hyperlipidemia and/or hypertension was defined as the date the person first met criteria for either of these conditions.

RESULTS

Description of the Olmsted County population

The REP Census identified 129,311 Olmsted County, MN residents on January 1, 2000 compared with 124,277 individuals counted by the 2000 US Census (104.1%); 123,716 persons provided Minnesota research authorization for medical record research (95.7%) and were included in our analyses. A total of 17,655 people (14.3%) had 2 or more conditions at the baseline date and 9,368 (7.6%) had 3 or more conditions (prevalent multimorbidity). Overall, we observed a total of 1,334,906 person-years of follow-up; however, as expected, the length of follow-up varied by age group. For example, median follow-up was 13.1 years in persons aged 0 to 19 years at baseline, 12.3 years in persons aged 70 to 79 years at baseline, and 4.9 years in persons aged 80 years or older at baseline.

Figure 1 and Supplementary Table C report the incidence of each of the 20 chronic conditions considered separately by age and sex. The incidence of most of the chronic conditions increased steeply with older age. However, the incidence of asthma,

substance abuse disorders, hepatitis, autism spectrum disorder, and infection with human immunodeficiency virus was higher in the younger population compared to persons older than 60 years. The incidence of depression increased from ages 0-19 to 20-39 years, declined from 40-49 to 60-69 years, and increased sharply again thereafter. The incidence of most conditions was higher in men compared to women of the same age; however, women had a higher incidence of depression, arthritis, asthma, and osteoporosis. The incidence curves in men and women crossed at age 50-59 years for cancer and at age 60-69 years for chronic obstructive pulmonary disease (Figure 1).

Incidence of multimorbidity by age, sex, and ethnicity

Figure 2 shows the age-specific incidence rates of multimorbidity in men and women separately (panels A and C), and in three ethnic groups (panels B and D). Both the incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased steeply with older age (Table 1, Table 2, and Figure 2). For example, the incidence of 2 chronic conditions in men was 6.5/1,000 person-years in persons who were ages 0-19 years, and 260.0/1,000 in persons who were ≥ 80 years. The overall incidence of 2 chronic conditions was slightly higher in women compared to men (overall standardized incidence rates 38.8 vs. 35.5/1,000 person-years; Table 1). The incidence of 2 chronic conditions was higher in Blacks compared to Whites, but lower in Asians compared to Whites (see standardized incidence rates in Table 1 and Figure 2). We observed similar patterns for the development of 3 chronic conditions (see standardized incidence rates in Table 2 and Figure 2). The overall incidence of 3 conditions was similar in men

and women (standardized incidence rates 25.5/1,000 person-years in men vs. 26.6/1,000 person-years in women); however, it was higher in Blacks and lower in Asians, compared to Whites (Figure 2).

In the set of sensitivity analyses in which we combined hyperlipidemia and hypertension as a single condition, we observed a slight decrease in the incidence of 2 chronic conditions and of 3 chronic conditions compared with the primary analyses. The overall incidence rate of 2 conditions decreased from 35.0 to 34.0/1,000 person-years in men and from 40.3 to 40.0/1,000 person-years in women. The incidence rate of 3 conditions decreased from 24.7 to 22.5/1,000 person-years in men and from 28.5 to 27.0/1,000 person-years in women (incidence rates non-standardized; data not shown in the Tables). For both 2 and 3 conditions, the decrease in incidence was more sizeable in men than in women.

Incidence of dyads and triads

Table 3 shows the incidence of the most common dyads or triads of chronic conditions in seven age strata and for men and women separately. As expected, the incidence of dyads and triads varied extensively with age. For example, the most common incident dyad in persons 0-19 years was depression and asthma (1.8/1,000 person-years in boys or men and 2.9/1,000 person-years in girls or women). By comparison, the most common dyad in persons ≥ 80 years was hypertension and cancer in men (18.9/1,000 person-years) and hypertension and arthritis in women (27.7/1,000 person-years). Similarly, the most common incident triad of conditions in persons aged 0-19 years was depression, asthma, and substance abuse disorders in both sexes. By comparison, the

most common incident triads in persons ≥ 80 years were hypertension, cancer, and arrhythmia in men and hyperlipidemia, hypertension, and arthritis in women.

As expected, the incidence of dyads and triads also varied by sex. In some instances, the composition of the dyads or triads was the same for men and women, but the magnitude of the incidence rate was different. In other instances, the magnitude of the incidence rate was similar in men and women, but the composition of the dyads and triads varied by sex. For example, the most common incident dyad in persons aged 60-69 years was hyperlipidemia and hypertension in both sexes, but the incidence rate was higher in men compared to women (23.4/1,000 person-years vs. 18.8/1,000 person-years). By contrast, the incidence rates of the most common triads in persons aged 60-69 years were similar in men and women (11.6/1,000 vs. 10.3/1,000 person-years); however, they included different conditions (Table 3).

DISCUSSION

Statement of the principal findings

The burden of multimorbidity in the United States is high and is increasing with an aging population and with improvements in survival. We leveraged a unique longitudinal data resource covering an entire, stable, and geographically defined population to examine the incidence of multimorbidity across all ages. The incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased steeply with older age, and the overall risk was similar in men and women. However, the number of people who developed multimorbidity before age 65 was more than four times greater than the number of people who developed multimorbidity after age 65. The incidence of

multimorbidity was highest in Blacks, and lowest in Asians. Finally, as expected, the combinations of conditions in incident dyads and triads differed extensively by age and by sex. These results have important implications for identifying individuals at higher risk of developing multimorbidity at different ages. These data are also a first step toward understanding the causes and the consequences of multimorbidity.

Strengths and limitations

A unique strength of our study was the ability to measure the incidence of multimorbidity documented in medical records across seven age groups and for an entire, geographically defined population. We used historical data both to exclude individuals with prevalent multimorbidity at baseline and to follow individuals over a long period of time to accurately document the development of incident multimorbidity. In total, our findings reflect 19 years of data accumulation (5 years before and 14 years after the baseline date).

Unfortunately, there is no standard definition of multimorbidity. Previous studies have included a wide range of chronic conditions and a wide range of time frames. We defined multimorbidity using the 20 conditions selected by US-DHHS which were chosen because they "meet the definition for chronicity, are prevalent [common], and are potentially amenable to public health or clinical interventions or both." [23] However, this definition provides equal weight to each of the 20 conditions without considering the impact of combinations of specific conditions on the quality of life of patients, the complexity of their joint management, and the severity of their long-term outcomes. In addition, this list does not include a number of conditions that may have a significant

impact on the burden of multimorbidity in older subjects (e.g., hearing and vision problems). Such conditions should be considered in future studies of multimorbidity. By contrast, the list includes some conditions that were less common in the general population. For example, autism appeared as part of an incident dyad in only 31 persons, and HIV infection in only 41 persons. Therefore, further efforts are needed to refine the list of the most relevant conditions to study multimorbidity, recognizing that the most relevant conditions will vary depending on the age and sex of the population.

Some of the dyads and triads derived by the combination of the 20 conditions selected by the US-DHHS may have a much stronger impact on the complexity of clinical management than others.[27] Therefore, some dyads or triads may be particularly costly for the health system, harder for the patient to manage by themselves, less amenable to a single disease approach to care (e.g., telemonitoring for heart failure), and may have a stronger effect on functionality, severity of symptoms, and risk of death. In addition, social factors (e.g., inadequate insurance, low education) and behavioral factors (e.g., poor diet) not reflected in the list of 20 US-DHHS conditions may be as important, or more important, than the 20 conditions in determining the complexity of clinical management and long-term outcomes.[27]

For example, because hyperlipidemia and hypertension are typically asymptomatic, and are often diagnosed as the result of routine screening, their combination is likely to have a much lower impact on the life of the patient than the combination of schizophrenia and heart failure. However, both combinations are considered multimorbidity by the US-DHHS definition. Our sensitivity analyses highlight this problem. As expected, when hyperlipidemia and hypertension were considered as

a single condition, the overall incidence of multimorbidity decreased. The decreases were relatively small but were more sizeable in men than in women. These findings emphasize the importance of reaching consensus on the list of conditions to be used to define multimorbidity. However, it is difficult to assess the utility of the 20 conditions included in the US-DHHS list without also understanding how different combinations of these conditions impact long term outcomes. Therefore, we plan to continue this initial incidence study with further analyses to assess which combinations of conditions have the greatest impact on adverse outcomes, including patient quality of life and complexity of clinical management. [27]

We defined incident multimorbidity as the date on which a person met the criteria for a second condition or for a third condition. We used an approach similar to that used in the definition for the onset of metabolic syndrome (reaching three of five components of the syndrome). [28,29] This simple operational definition of incident multimorbidity should be easy to replicate, and should facilitate future comparisons with other populations.

Potential limitations of our study include the inability to validate the ICD-9 codes. It was not possible to confirm all diagnoses for the entire study population, and some ICD-9 codes may have been assigned in error (e.g., “rule out” diagnostic codes). To reduce the likelihood of a single ICD-9 code error, we required two or more diagnosis codes separated by more than 30 days for a person to be defined as having a condition. [30] However, if a person received a valid code and was lost to follow-up or died rapidly after diagnosis, we may have underestimated the incidence of some of the conditions.

In addition, we used diagnosis date as a proxy for the true date of onset of the condition.

Some individuals may have moved into Olmsted County after having been diagnosed with one or more chronic conditions elsewhere. If those persons continued to receive care within the REP for a number of years, we captured their chronic condition at the time of subsequent health care visits. However, we did not know the true date of onset for the condition, and the sequence of accumulation of conditions could be distorted. Because the population of Olmsted County is stable, particularly among persons who are 40 years of age or older, [19] we do not expect a major distortion of the multimorbidity incidence rates observed in this study due to migration.

Finally, our study focused on a single geographically defined US population, and the incidence of multimorbidity may differ in other populations. However, the demographic and socioeconomic characteristics of our population are similar to those of the upper Midwest of the United States, [20] and the prevalence of multimorbidity in persons 65 years of age or older was similar in our population compared with the entire US Medicare population. [16] Replication of this study in other populations in the United States and worldwide will allow for useful comparisons. [31]

Comparison with other studies

A number of studies have described the prevalence of multimorbidity in various populations; [1,7-12] however, few studies have described the incidence of multimorbidity, and no incidence studies are available for the US. In 1998, Van den Akker and colleagues estimated the one year incidence of multimorbidity in patients from a

network of family practices in the Netherlands. [32] Incident multimorbidity was defined as the new development of at least 2 of 335 diagnostic categories within a one year period. Overall, 7.9% of their population developed one new disease and 1.3% developed two or more new diseases in one year. The proportion of people who developed two or more new conditions increased with older age, but did not differ substantially by sex. It is difficult to compare our results directly to the Dutch findings because of methodological differences (e.g., number of conditions considered and time frame), and because it is not clear whether some of the participants in the Dutch study already had one or more conditions at baseline. However, we observed similar patterns of increasing incidence with older age, and limited differences between men and women in overall incidence.

More recently, Melis and colleagues assessed the incidence of multimorbidity in Swedish people aged 75 years or older at baseline who participated in a longitudinal cohort study. [33] Incident multimorbidity was defined as the development of at least 2 of 39 chronic conditions during three years of follow-up. Participants with none of the 39 chronic conditions at baseline had a multimorbidity incidence rate of 12.6 per 100 person-years, and patients with one of the 39 conditions at baseline had an incidence rate of 32.9 per 100 person-years. Although we examined fewer conditions than the Swedish group (20 vs. 39), and the ascertainment of incident conditions was different (medical records data vs. survey methods), our incidence rates of multimorbidity in subjects aged 75 years or older were similar (19.1 per 100 person-years in people with no conditions at baseline and 38.9 per 100 person-years in persons with one condition at baseline; both sexes combined; data not shown).

Meaning of the study

To understand the importance of these findings, we draw an analogy with the difference between prevalence and incidence in epidemiologic studies considering one disease at a time. [34,35] Incidence is the direct measure of the risk of people to develop a given disease, whereas prevalence is the percent of people affected by the same disease at one point in time, and reflects both the effect of incidence and the effect of survival after the onset of the disease. [34,35] Similarly, the prevalence of multimorbidity gives us a static picture of the population; however, prevalence may be misleading when studying the mechanisms of multimorbidity. For example, a higher prevalence of multimorbidity in women than in men may be due to a higher risk of women developing multimorbidity, or to a longer survival of women affected by multimorbidity. [16] Similarly, studying outcomes among persons with prevalent multimorbidity may be clinically relevant, but may not clarify the outcomes of multimorbidity at the population level (e.g., survival bias and inability to study the effect of the duration of multimorbidity).

Prior studies of the prevalence of multimorbidity have shown a dramatic increase in the number of people living with 2 or more chronic conditions at older ages. [1,7-11] However, the high prevalence of multimorbidity in the older population implies that relatively few older individuals remain at risk of developing multimorbidity. Overall, among persons aged 80 years or older at baseline, only 891 out of 3,710 (24.0%) were at risk of developing 2 chronic conditions (the other 76.0% already had 2 or more of the 20 conditions). Although the persons who reached 80 years of age or older and

remained free of multimorbidity were a particularly resilient group, they had a higher risk of developing subsequent multimorbidity than younger persons.

We also found that the total number of people who developed multimorbidity before age 65 years was more than 4 times greater than the number of people who developed multimorbidity at ages 65 or older (28,378 vs. 6,214). These data emphasize the need to target preventive efforts at much younger ages, but represent only a first step toward future research to identify the social, behavioral, and clinical risk and protective factors for multimorbidity.

We found important differences in the incidence of multimorbidity by ethnicity. The age standardized incidence rates of multimorbidity were higher in Blacks and lower in Asians compared to Whites. Our findings are consistent with previous studies that showed a higher prevalence of multimorbidity in Blacks compared to Whites, but a lower prevalence of multimorbidity in Asians. [8,16,36-38] Our data suggest that some of these differences in prevalence may be attributed to differences in the incidence of the conditions among different ethnic groups. However, differential survival may also contribute to the differences in prevalence. In turn, both differences in incidence and in prevalence may be influenced by socioeconomic factors, lifestyle behaviors, social environment, and healthcare access. Further research is needed to better characterize these disparities and to identify the causal mechanisms that contribute to different development of chronic conditions and to different survival.

As expected, the incidence and the composition of the dyads and triads of conditions varied extensively across age and sex strata. For example, women 20 years of age or older were more likely to have depression as a component of their incident

multimorbidity dyads and triads compared to men. Such differences may lead to different long-term outcomes in men and women. Therefore, these data are useful to understand how multimorbidity develops, and are an important first step toward future research. In particular, such incident data are necessary to study the chronological order of acquisition of multiple chronic conditions in different age, sex, and ethnic strata. Incidence data are also necessary to determine whether the differential order of acquisition is associated with a different risk of adverse long-term outcomes such as hospitalizations, emergency department visits, or death. For example, it is not clear whether acquiring depression prior to arthritis results in worse long-term outcomes compared with acquiring arthritis prior to depression. Future studies are also needed to understand how additional chronic conditions accumulate after the development of a second and third condition. Finally, the incidence of specific dyads and triads reflects the incidence of the individual conditions in specific age and sex groups. Many of these dyads and triads are expected to develop simply by chance. Therefore, future studies are needed to identify the dyads and triads that co-occur beyond chance. Identification of incident dyads and triads that reflect shared etiologic mechanisms or shared risk factors may lead to combined treatment or prevention strategies.

Conclusions and clinical implications

It is important and urgent to understand the causes and the consequences of multimordibity to inform efforts to delay and prevent disease onset and to develop effective strategies for caring for patients with multimorbidity. We studied the incidence of multimorbidity across all ages, separately in men and women, and in three ethnic

groups in a geographically defined US population. The incidence of multimorbidity increased steeply with older age and was higher in Blacks but lower in Asians compared to Whites. Men and women had a similar overall risk, but the combinations of conditions within dyads and triads varied extensively by age and by sex. These data represent an important first step toward identifying conditions which co-occur more frequently than chance alone, identifying specific risk factors for multimorbidity, understanding how chronic conditions accumulate over time, and toward identifying combinations of conditions that predict adverse outcomes.

Competing interest declaration:

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have support from any companies for the submitted work; (2) none of the authors have any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have any non-financial interests that may be relevant to the submitted work.

Contributorship statement: Dr. St. Sauver had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor for the study.

Study concept and design: St. Sauver, Boyd, Grossardt, Yawn, Rocca.

Acquisition, analysis, or interpretation of data: St. Sauver, Grossardt, Rocca.

Drafting of the manuscript: St. Sauver, Rocca.

Critical revision of the manuscript for important intellectual content: St. Sauver, Boyd, Grossardt, Bobo, Finney Rutten, Roger, Ebbert, Therneau, Yawn, and Rocca.

Statistical analysis: Grossardt, Therneau.

Obtained funding: Yawn, Rocca.

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

Study supervision: Yawn, Rocca.

Identifiable patients: No identifiable patients were included.

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Transparency declaration: The lead author (the manuscript's guarantor, Dr. JLS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1. Incidence of the second of two chronic conditions (per 1,000 person-years) in persons living in Olmsted County, MN by age, sex, and ethnicity.

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
All ethnic groups						
0-19	18,879	140,653	6.5 (921)	18,024	134,725	8.5 (1,151)
20-39	27,732	151,734	17.2 (2,613)	28,571	158,252	25.1 (3,972)
40-49	16,396	82,324	43.6 (3,590)	16,713	85,660	45.8 (3,920)
50-59	11,779	52,085	85.2 (4,436)	12,398	55,270	84.6 (4,674)
60-69	5,218	19,653	139.4 (2,739)	5,603	21,246	135.3 (2,874)
70-79	1,775	5,451	209.9 (1,144)	2,184	6,660	202.0 (1,345)
≥ 80	531	1,589	260.0 (413)	1,016	2,887	277.1 (800)
0-64	50,648	439,254	29.7 (13,059)	51,056	447,399	34.2 (15,319)
≥ 65	3,794	14,236	196.5 (2,797)	4,636	17,300	197.5 (3,417)
All ages	52,479	453,489	35.0 (15,856)	53,582	464,699	40.3 (18,736)
Standardized†	---	---	35.5	---	---	38.8
Blacks						
0-19	877	6,411	5.5 (35)	749	5,362	6.0 (32)
20-39	1,099	6,178	16.5 (102)	934	5,647	23.0 (130)
40-49	429	1,836	63.2 (116)	324	1,392	61.8 (86)
50-59	180	683	105.3 (72)	139	513	121.0 (62)
60-69	60	223	134.8 (30)	47	150	193.2 (29)
70-79	18	71	140.1 (10)	23	60	200.4 (12)
≥ 80	4	11	274.0 (3)	3	5	580.3 (3)
0-64	1,848	15,240	22.0 (335)	1,563	13,010	25.5 (332)
≥ 65	48	173	190.8 (33)	37	118	185.7 (22)
All ages	1,873	15,413	23.9 (368)	1,587	13,128	27.0 (354)
Standardized†	---	---	38.9	---	---	48.5
Asians						
0-19	818	6,331	3.5 (22)	826	6,299	5.6 (35)
20-39	1,090	6,372	15.1 (96)	1,168	7,167	14.6 (105)
40-49	534	2,464	39.8 (98)	591	2,869	33.8 (97)
50-59	339	1,588	71.8 (114)	376	1,687	79.4 (134)
60-69	159	592	120.0 (71)	185	570	161.3 (92)
70-79	51	163	140.8 (23)	74	177	271.6 (48)
≥ 80	21	60	216.6 (13)	40	92	358.1 (33)
0-64	1,897	17,137	21.6 (370)	1,997	18,399	23.3 (429)
≥ 65	114	433	154.7 (67)	159	463	248.4 (115)
All ages	1,954	17,571	24.9 (437)	2,105	18,862	28.8 (544)
Standardized†	---	---	29.5	---	---	34.9
Whites						
0-19	14,956	119,686	6.8 (818)	14,414	114,906	9.0 (1,032)
20-39	21,792	128,801	17.9 (2,303)	23,214	135,903	26.5 (3,599)
40-49	14,426	74,921	43.6 (3,269)	15,088	79,123	46.1 (3,646)
50-59	10,795	48,361	85.8 (4,149)	11,520	51,901	84.8 (4,399)

Table 1. Continued

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
60-69	4,823	18,362	140.4 (2,578)	5,221	20,075	134.7 (2,704)
70-79	1,653	5,090	212.6 (1,082)	2,030	6,301	200.9 (1,266)
≥ 80	497	1,495	262.8 (393)	953	2,754	274.5 (756)
0-64	40,703	383,410	31.2 (11,952)	42,149	394,566	35.9 (14,170)
≥ 65	3,517	13,306	198.4 (2,640)	4,317	16,398	197.1 (3,232)
All ages	42,382	396,716	36.8 (14,592)	44,465	410,964	42.3 (17,402)
Standardized†	---	---	36.0	---	---	39.4

* Incidence rates are reported per 1,000 person-years.
† Incidence rates were directly standardized to the total US population from the 2010 US Decennial Census after removing the number of people with prevalent multimorbidity (≥ 2 chronic conditions) as projected from our previous study (see Supplementary Table B).[16]

Table 2. Incidence of the third of three chronic conditions (per 1,000 person-years) in persons living in Olmsted County, MN by age, sex, and ethnicity.

	Men			Women		
Ethnicity age (years)	**Persons**	**Person-years**	**Incidence rate* (n)**	**Persons**	**Person-years**	**Incidence rate* (n)**
All ethnic groups						
0-19	19,029	144,025	1.3 (186)	18,203	138,055	2.0 (282)
20-39	28,721	162,693	6.9 (1,123)	30,135	177,878	10.9 (1,944)
40-49	17,901	95,582	22.6 (2,157)	18,824	103,400	24.2 (2,507)
50-59	14,398	69,907	52.8 (3,688)	15,475	76,247	51.5 (3,930)
60-69	7,517	31,617	99.5 (3,146)	8,313	35,342	96.7 (3,416)
70-79	3,109	10,639	169.7 (1,805)	3,899	13,653	156.4 (2,136)
≥ 80	992	3,230	218.9 (707)	1,970	6,414	230.6 (1,479)
0-64	53,073	491,536	18.0 (8,852)	54,280	517,164	20.2 (10,432)
≥ 65	5,938	26,156	151.4 (3,960)	7,706	33,825	155.6 (5,262)
All ages	55,898	517,693	24.7 (12,812)	58,450	550,989	28.5 (15,694)
Standardized†	---	---	25.5	---	---	26.6
Blacks						
0-19	879	6,530	1.1 (7)	751	5,458	1.1 (6)
20-39	1,123	6,428	8.6 (55)	960	6,032	9.4 (57)
40-49	460	2,126	34.8 (74)	373	1,723	41.2 (71)
50-59	218	952	69.3 (66)	173	737	69.2 (51)
60-69	81	312	96.1 (30)	70	241	132.8 (32)
70-79	27	108	129.4 (14)	28	84	191.0 (16)
≥ 80	5	23	172.3 (4)	5	9	321.2 (3)
0-64	1,883	16,227	13.3 (216)	1,602	14,101	14.5 (205)
≥ 65	58	252	135.1 (34)	54	183	169.2 (31)
All ages	1,911	16,479	15.2 (250)	1,633	14,284	16.5 (236)
Standardized†	---	---	28.2	---	---	34.8
Asians						
0-19	823	6,419	0.6 (4)	832	6,442	1.6 (10)
20-39	1,109	6,747	6.2 (42)	1,206	7,587	4.6 (35)
40-49	574	2,841	18.7 (53)	651	3,327	20.7 (69)
50-59	390	1,942	44.8 (87)	439	2,191	46.1 (101)
60-69	203	830	78.3 (65)	254	966	97.3 (94)
70-79	80	259	138.8 (36)	110	353	141.5 (50)
≥ 80	32	84	202.0 (17)	84	228	241.2 (55)
0-64	1,940	18,472	12.2 (225)	2,074	20,167	12.9 (261)
≥ 65	165	650	121.5 (79)	258	929	164.7 (153)
All ages	2,027	19,122	15.9 (304)	2,235	21,096	19.6 (414)
Standardized†	---	---	21.1	---	---	23.2
Whites						
0-19	15,088	122,717	1.3 (160)	14,576	117,885	2.2 (259)
20-39	22,681	138,725	7.1 (990)	24,638	154,160	11.7 (1,799)
40-49	15,811	87,199	22.7 (1,978)	17,025	95,693	24.1 (2,308)
50-59	13,262	65,243	53.1 (3,464)	14,443	71,770	51.7 (3,714)

Table 2. Continued

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
60-69	7,028	29,816	100.8 (3,005)	7,796	33,477	96.9 (3,244)
70-79	2,930	10,061	171.9 (1,729)	3,680	13,006	157.2 (2,045)
≥ 80	942	3,093	219.5 (679)	1,848	6,105	231.0 (1,410)
0-64	42,953	432,089	19.0 (8,213)	45,157	459,919	21.2 (9,761)
≥ 65	5,572	24,764	153.1 (3,792)	7,224	32,177	155.9 (5,018)
All ages	45,583	456,853	26.3 (12,005)	49,033	492,097	30.0 (14,779)
Standardized†	---	---	25.7	---	---	27.0

***** Incidence rates are reported per 1,000 person-years.
† Incidence rates were directly standardized to the total US population from the 2010 US Decennial Census after removing the number of people with prevalent multimorbidity (≥ 3 chronic conditions) as projected from our previous study (see Supplementary Table B).[16]

Table 3. Incidence rates (per 1,000 person-years) and composition of the most common dyads and triads of chronic conditions in persons living in Olmsted County, MN by age and sex.

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
0 – 19								
1	DEP - AST	1.8 (257)	DEP - AST	2.9 (395)	DEP - AST - SUB	0.4 (53)	DEP - AST - SUB	0.4 (62)
2	DEP - SUB	1.3 (178)	DEP - SUB	1.8 (240)	DEP - AST - COPD	0.1 (17)	DEP - AST - COPD	0.3 (39)
3	AST - COPD	0.9 (122)	AST - COPD	0.7 (91)	DEP - SUB - SZO	0.1 (8)	DEP - ARR - AST	0.2 (27)
4	AST - SUB	0.4 (56)	DEP - ARR	0.4 (50)	LIP - DEP - AST	<0.1 (7)	DEP - ARR - SUB	0.1 (13)
5	DEP - ARR	0.1 (21)	DEP - COPD	0.4 (48)	3-way tie ‖	< 0.1 (6)	DEP - SUB - COPD	0.1 (12)
20 – 39								
1	DEP - SUB	3.5 (525)	DEP - AST	3.4 (531)	DEP - AST - SUB	0.4 (73)	DEP - AST - SUB	0.8 (134)
2	LIP - HTN	1.4 (207)	DEP - SUB	2.9 (463)	DEP - SUB - SZO	0.4 (69)	DEP - AST - COPD	0.7 (121)
3	DEP - AST	1.1 (174)	DEP - CAN	2.0 (309)	LIP - HTN - DIA	0.4 (65)	DEP - ARR - AST	0.4 (77)
4	LIP - DEP	1.0 (155)	LIP - DEP	1.7 (267)	DEP - ARR - SUB	0.3 (46)	DEP - SUB - COPD	0.3 (61)
5	LIP - DIA	0.9 (137)	DEP - ARR	1.4 (222)	LIP - HTN - DEP	0.3 (45)	LIP - DEP - AST	0.3 (58)
40 – 49								
1	LIP - HTN	7.0 (580)	LIP - DEP	4.1 (354)	LIP - HTN - DIA	3.1 (294)	LIP - HTN - DIA	1.4 (147)
2	LIP - DIA	4.4 (363)	LIP - HTN	3.6 (308)	LIP - HTN - DEP	1.2 (115)	LIP - HTN - DEP	1.1 (114)
3	LIP - DEP	3.5 (285)	DEP - ART	2.6 (224)	LIP - HTN - ART	0.9 (84)	LIP - DEP - DIA	1.0 (99)
4	LIP - ART	2.4 (198)	DEP - CAN	2.6 (224)	LIP - HTN - CAD	0.9 (83)	LIP - DEP - ART	0.8 (84)
5	DEP - SUB	1.9 (157)	HTN - DEP	2.4 (203)	LIP - DEP - DIA	0.8 (74)	LIP - DEP - AST	0.6 (63)
50 – 59								
1	LIP - HTN	14.5 (757)	LIP - HTN	9.8 (540)	LIP - HTN - DIA	7.2 (504)	LIP - HTN - DIA	3.9 (300)
2	LIP - DIA	8.7 (455)	LIP - ART	6.5 (359)	LIP - HTN - ART	3.5 (242)	LIP - HTN - ART	3.0 (232)
3	LIP - ART	6.7 (351)	LIP - DEP	5.9 (325)	LIP - HTN - CAD	3.0 (208)	LIP - HTN - DEP	2.4 (185)
4	LIP - CAN	4.6 (241)	DEP - ART	4.8 (265)	LIP - HTN - DEP	1.9 (131)	LIP - DEP - ART	2.4 (180)
5	HTN - DIA	4.4 (227)	LIP - CAN	4.5 (246)	LIP - HTN - ARR	1.7 (117)	LIP - HTN - CAN	1.8 (136)

Table 3. Continued 1

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
60 – 69								
1	LIP - HTN	23.4 (460)	LIP - HTN	18.8 (400)	LIP - HTN - DIA	11.6 (366)	LIP - HTN - ART	10.3 (363)
2	LIP - DIA	11.5 (226)	LIP - ART	15.5 (330)	LIP - HTN - ART	6.8 (214)	LIP - HTN - DIA	7.4 (263)
3	LIP - ART	11.4 (224)	HTN - ART	10.4 (220)	LIP - HTN - CAD	6.3 (200)	LIP - HTN - CAN	4.6 (164)
4	LIP - CAN	10.0 (196)	LIP - CAN	6.8 (145)	LIP - HTN - CAN	4.9 (155)	LIP - ART - CAN	2.9 (102)
5	HTN - DIA	8.6 (169)	LIP - DIA	6.4 (135)	LIP - HTN - ARR	3.4 (106)	LIP - DIA - ART	2.7 (95)
6	HTN - ART	7.7 (152)	ART - CAN	4.9 (105)	LIP - DIA - ART	2.9 (91)	LIP - HTN - DEP	2.6 (93)
7	LIP - CAD	6.9 (136)	LIP - OST	4.9 (105)	LIP - ART - CAN	2.6 (82)	LIP - DEP - ART	2.5 (89)
8	HTN - CAN	6.2 (121)	HTN - CAN	4.8 (103)	LIP - DIA - CAD	2.4 (76)	LIP - ART - ARR	2.3 (83)
9	ART - CAN	4.5 (89)	HTN - DIA	4.6 (97)	HTN - DIA - ART	2.2 (71)	LIP - HTN - OST	2.2 (79)
10	LIP - ARR	4.5 (88)	LIP - DEP	4.4 (94)	LIP - ARR - CAD	2.2 (68)	HTN - DIA - ART	2.2 (77)
70 – 79								
1	LIP - HTN	19.1 (104)	LIP - HTN	26.0 (173)	LIP - HTN - CAN	11.9 (127)	LIP - HTN - ART	15.7 (214)
2	HTN - CAN	18.9 (103)	HTN - ART	18.5 (123)	LIP - HTN - DIA	10.4 (111)	LIP - HTN - DIA	9.8 (134)
3	LIP - CAN	15.0 (82)	LIP - ART	15.5 (103)	LIP - HTN - CAD	9.7 (103)	LIP - HTN - CAN	6.0 (82)
4	HTN - ART	13.2 (72)	LIP - OST	9.0 (60)	LIP - HTN - ART	9.4 (100)	LIP - ART - CAN	5.4 (74)
5	ART - CAN	11.6 (63)	HTN - CAN	8.9 (59)	LIP - HTN - ARR	5.5 (58)	HTN - ART - CAN	5.2 (71)
6	LIP - ART	11.6 (63)	HTN - OST	8.3 (55)	HTN - ART - CAN	4.9 (52)	LIP - ART - OST	5.2 (71)
7	HTN - DIA	10.1 (55)	ART - CAN	8.1 (54)	LIP - ART - CAN	4.7 (50)	LIP - HTN - OST	4.6 (63)
8	HTN - ARR	9.9 (54)	ART - OST	7.8 (52)	HTN - CAN - ARR	4.2 (45)	LIP - HTN - ARR	4.5 (62)
9	LIP - CAD	7.7 (42)	HTN - DIA	7.8 (52)	HTN - ART - ARR	4.1 (44)	HTN - ART - OST	4.0 (55)
10	LIP - DIA	7.7 (42)	LIP - CAN	7.8 (52)	LIP - DIA - CAN	4.1 (44)	2-way tie ¶	3.4 (47)
≥ 80								
1	HTN - CAN	18.9 (30)	HTN - ART	27.7 (80)	HTN - CAN - ARR	8.7 (28)	LIP - HTN - ART	10.3 (66)
2	HTN - ARR	17.6 (28)	LIP - HTN	23.2 (67)	LIP - HTN - CAN	7.7 (25)	HTN - ART - OST	9.8 (63)
3	HTN - ART	14.5 (23)	HTN - ARR	17.7 (51)	HTN - ART - CAN	7.4 (24)	HTN - ART - CAN	9.2 (59)

Table 3. Continued 2

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
4	ART - ARR	12.0 (19)	HTN - CAN	15.2 (44)	LIP - HTN - ART	6.2 (20)	HTN - ART - ARR	9.0 (58)
5	CAN - ARR	12.0 (19)	HTN - OST	14.9 (43)	LIP - HTN - ARR	5.9 (19)	LIP - HTN - OST	5.9 (38)
6	HTN - CAD	10.1 (16)	HTN - DEM	11.8 (34)	ART - CAN - ARR	5.3 (17)	LIP - HTN - DIA	5.0 (32)
7	LIP - HTN	10.1 (16)	ART - CAN	10.0 (29)	HTN - ART - ARR	5.3 (17)	LIP - HTN - ARR	4.7 (30)
8	ART - CAN	8.8 (14)	ART - OST	9.7 (28)	HTN - CAN - CAD	5.0 (16)	LIP - HTN - CAN	4.5 (29)
9	CAN - CAD	8.8 (14)	HTN - CKD	7.6 (22)	LIP - HTN - CAD	5.0 (16)	ART - CAN - OST	4.4 (28)
10	HTN - DEM	8.8 (14)	3-way tie **	7.3 (21)	LIP - ART - CAN	4.6 (15)	LIP - HTN - CAD	3.9 (25)

* Rank order from the most frequent to the least frequent incident dyad or triad. For the younger age groups (through age 59 years), we reported the 5 most frequent incident combinations; for the older age groups (60 years and older), we reported the 10 most frequent incident combinations.

† Definition of acronyms in order of frequency: LIP = hyperlipidemia; HTN = hypertension; DEP = depression; DIA = diabetes; ART = arthritis; CAN = cancer; ARR = cardiac arrhythmias; AST = asthma; CAD = coronary artery disease; SUB = substance abuse disorders; COPD = chronic obstructive pulmonary disease; OST = osteoporosis; CKD = chronic kidney disease; STR = stroke; CHF = congestive heart failure; DEM = dementia; SZO = schizophrenia; HEP = hepatitis; AUT = autism spectrum disorder; and HIV = human immunodeficiency virus.

‡ Incidence rates per 1,000 person years. Rates can be calculated by dividing the number of incident persons in parentheses by the person- years at risk of 2 conditions from each age- and sex-specific stratum for all ethnic groups combined in Table 1.

§ Incidence rates per 1,000 person years. Rates can be calculated by dividing the number of incident persons in parentheses by the person-years at risk of 3 conditions from each age- and sex-specific stratum for all ethnic groups combined in Table 2.

‖ Three-way tie for the rank 5 triad in men ages 0-19 years: 1) AST-SUB-COPD; 2) DEP-ARR-SUB; 3) DEP-AST-DEM.

¶ Two-way tie for the rank 10 triad in women ages 70-79 years: 1) HTN-ART-ARR; 2) LIP-CAN-OST.

** Three-way tie for the rank 10 dyad in women ages ≥ 80 years: 1) ART-ARR; 2) HTN-DIA; 3) LIP-ART.

Figure Legends

Figure 1. Age- and sex-specific incidence rates (per 1,000 person-years) of the 20 chronic conditions considered separately. The 20 panels are presented by rows in decreasing order of frequency (by overall age- and sex-standardized prevalence). [16]

Figure 2. Incidence rates (per 1,000 person-years) of 2 chronic conditions (second condition in a dyad) and of 3 chronic conditions (third condition in a triad) in men and women separately (panels A and C), and stratified by ethnicity (panels B and D).

Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity

Jennifer L. St. Sauver *associate professor* [1 2], Cynthia M. Boyd *associate professor* [3], Brandon R. Grossardt *biostatistician* [4], William V. Bobo *assistant professor* [5], Lila J. Finney Rutten *associate professor* [1 2], Véronique L. Roger *professor* [1 2 6], Jon O. Ebbert *professor* [2], Terry M. Therneau *professor* [4], Barbara P. Yawn *director of research* [1 7], Walter A. Rocca *professor* [1 8]

Author Affiliations: [1] Division of Epidemiology, Department of Health Sciences Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [2] The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [3] Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287, USA; [4] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [5] Department of Psychiatry and Psychology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [6] Division of Cardiovascular Diseases, Department of Internal Medicine, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; [7] Department of Research, Olmsted Medical Center, 210 Ninth Street SE, Rochester, MN 55904, USA; [8] Department of Neurology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

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Corresponding Author: Walter A. Rocca, MD, MPH, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (telephone: 507-284-3568; fax: 507-284-1516; e-mail: rocca@mayo.edu).

Extra material supplied by the author: Supplementary tables A-C

ABSTRACT

Objective: To study the incidence of de novo multimorbidity across all ages in a geographically defined population with an emphasis on sex and ethnic differences.

Design: Historical cohort study.

Setting: All persons residing in Olmsted County, Minnesota, USA on January 1, 2000 who had not refused permission for their records to be used for research (n = 123,716).

Participants: We used the Rochester Epidemiology Project medical records-linkage system to identify all of the county residents. We identified and removed from the cohort all persons who had developed multimorbidity before January 1, 2000 (baseline date), and we followed the cohort over 14 years (January 1, 2000 through December 31, 2013).

Main outcome measures: Incident multimorbidity was defined as the development of the second of 2 conditions (dyads) from among the 20 chronic conditions selected by the United States Department of Health and Human Services. We also studied the incidence of the third of 3 conditions (triads) from among the 20 chronic conditions.

Results: The incidence of multimorbidity increased steeply with older age; however, the number of people with incident multimorbidity was substantially greater in people younger than 65 years compared to people age 65 years or older (28,378 vs. 6,214).

The overall risk was similar in men and women; however, the combinations of conditions (dyads and triads) differed extensively by age and by sex. Compared to Whites, the incidence of multimorbidity was higher in Blacks and lower in Asians.

Conclusions: The risk of developing de novo multimorbidity increases steeply with older age, varies by ethnicity, and is similar in men and women overall. However, **as expected**, the combinations of conditions vary extensively by age and sex. These data represent an important first step toward identifying the causes and the consequences of multimorbidity.

ARTICLE SUMMARY: Strengths and limitations of this study

- This is one of the first studies worldwide focusing on the incidence of multimorbidity rather than on the prevalence of multimorbidity. Prevalence reflects both the effect of incidence and of survival after the onset of multimorbidity. We used a simple definition of incident multimorbidity that can be replicated in other populations.
- This study covered an entire geographically defined population, and used a unique records-linkage system. Persons were followed historically over 14 years. None of the data were derived from self-report or interviews.
- Studies of multimorbidity require the definition of the number of conditions considered, of the time window of occurrence, and of the source of data (medical records vs. interview). We used the 20 conditions recommended by the United States Department of Health and Human Services. These 20 conditions represent a first consensus list; however, not all of the conditions have the same impact on the complexity of care or on the quality of life of patients.
- Potential limitations of this study include the uncertain validity of diagnostic codes, the possible incompleteness of information due to in or out migration, and the inability to generalize our findings to other populations with different demographic or social characteristics.
- Replication of this study in other populations in the United States and worldwide will allow for useful comparisons.

INTRODUCTION

The demographic expansion of the elderly population and the improvements in survival of people affected by chronic conditions have caused a dramatic rise in the number of people living with multimorbidity (≥ 2 chronic conditions). In the United States, the prevalence of multimorbidity among Medicare recipients increases from 62% at age 65 - 74 years to 82% at ages 85 years and older. [1] The monetary costs associated with managing patients with multiple chronic conditions are overwhelming. [2-4] In addition, fragmented health care in patients with multimorbidity causes a particularly high risk for complications and a lower quality of life. [5,6]

Several studies have described the prevalence of multimorbidity in a wide range of populations. [1,7-12] Additional studies have focused on how to manage patients with multiple chronic conditions. [13,14] However, in 2010 the United States Department of Health and Human Services (US-DHHS) highlighted the critical need to identify groups of individuals at higher risk of developing multimorbidity (first appearance of multimorbidity). Such studies of incident multimorbidity are essential to identify patterns of disease accumulation, and to identify the populations at high risk of developing multimorbidity. For example, multimorbidity is highly prevalent in the elderly; however, many of the processes that lead to multimorbidity begin at much earlier ages. Therefore, data on the ages at which multimorbidity begins and on the patterns of accumulation of conditions over time are urgently needed to develop focused interventions to prevent multimorbidities and their adverse health outcomes. [15]

Unfortunately, there are currently no population-based data on the incidence of multimorbidity in the United States across all ages, even though multimorbidity is a high

public health priority for the nation. [15] The Rochester Epidemiology Project (REP) medical records-linkage system captures long-term medical information on a stable population, and is therefore uniquely positioned to study the incidence of multimorbidity. In a previous paper, we described in detail the patterns of prevalent multimorbidity in this population. [16] In this study, we further leveraged this data resource to examine the incidence of multimorbidity across all ages, separately in men and women, and in three ethnic groups. [17]

METHODS

Study population

The REP has tracked and linked health care information for the population of Olmsted County, MN, since 1966.[17-19] The vast majority of medical care in this community is currently provided by a few health care institutions: Olmsted Medical Center and its affiliated hospital, Mayo Clinic and its two affiliated hospitals, the Rochester Family Medicine Clinic, and a few smaller care facilities. The health care records from these institutions are linked together through the REP records-linkage system. [17-19] Persons are considered residents of Olmsted County at the time of each health care visit based on their address. Over the years, this address information has been accumulated and is used to define who resided in Olmsted County at any given point in time since 1966 (REP Census). The population counts obtained by the REP Census are similar to those obtained by the US Census, indicating that virtually the entire population of the county is captured by the system. [18-20] We used the REP Census to identify all individuals who resided in Olmsted County on January 1, 2000 (baseline date); however, we included

only individuals who had not refused permission to use their medical records for research (Minnesota research authorization). [18,21,22]

Definition of incident multimorbidity

We focused on 20 selected chronic conditions recommended by the US-DHHS for studying multimorbidity. [23,24] The list of the 20 conditions and the corresponding ICD-9 codes used in this study are provided in Supplementary Table A. [23,24] We first identified all ICD-9 codes associated with these 20 chronic conditions that occurred in the population between January 1, 1995 and December 31, 1999 (5 years before the baseline date, January 1, 2000). Persons who did not have any ICD-9 code for a given condition were assumed to not have the condition of interest. By contrast, residents were defined as having a chronic condition if they had at least two ICD-9 codes for that condition separated by more than 30 days, and the incidence date was assigned at the time they received a second diagnostic code.

Persons who had 2 or more of the 20 conditions at baseline were considered to have prevalent multimorbidity and were therefore excluded from incidence analyses of 2 chronic conditions (dyads). Similarly, persons who had 3 or more of the 20 conditions at baseline were excluded from incidence analyses of 3 chronic conditions (triads). All persons in this fixed population cohort were followed historically through the REP records-linkage system for approximately 14 years to study the emergence of new conditions.

Statistical Analyses

All persons in the cohort were followed from January 1, 2000 through the last contact with the records-linkage system (the earliest of death date, last medical visit date, or December 31, 2013). The incidence of each of the 20 chronic conditions was calculated among persons free of that condition at baseline. Persons contributed person-years to the denominator for the incidence of 2 conditions (development of a second condition in a dyad) only during the time when they had 0 or 1 chronic conditions, whereas persons contributed person-years to the denominator for the incidence of 3 chronic conditions (development of a third condition in a triad) only when they had 0, 1, or 2 chronic conditions. Although the majority of people accumulated conditions one-at-a-time, some subjects jumped from 0 to 2 conditions, or from 1 to 3, or even from 0 to 3 conditions. For example, a person previously considered free of all of the 20 conditions who was diagnosed with hyperlipidemia, hypertension, and depression during one visit was counted as having three incident dyads and one incident triad on the same date.

Incidence rates were reported separately by age (using seven age strata or splitting the entire population in 0-64 and ≥ 65 years), sex, and ethnicity, and were directly standardized by age and sex to the total US 2010 Decennial Census after removing projected prevalence (see Supplementary Table B). Because the study covered the target population completely, and no sampling was involved, confidence intervals were not included in the tables. [25,26] Ethnicity data were not available for 9,176 people (7.4% of the cohort). These individuals were included in the overall and age- and sex-specific analyses, but not in the ethnicity-specific analyses.

Although the 20 conditions proposed by the US-DHHS represent a national consensus, [15] some of the conditions may have a different prognostic impact than others. For example, hyperlipidemia and hypertension often occur together and tend to remain asymptomatic. Therefore, we performed a set of sensitivity analyses combining hyperlipidemia and hypertension as a single chronic condition. The date of incidence for the single chronic condition of hyperlipidemia and/or hypertension was defined as the date the person first met criteria for either of these conditions.

RESULTS

Description of the Olmsted County population

The REP Census identified 129,311 Olmsted County, MN residents on January 1, 2000 compared with 124,277 individuals counted by the 2000 US Census (104.1%); 123,716 persons provided Minnesota research authorization for medical record research (95.7%) and were included in our analyses. A total of 17,655 people (14.3%) had 2 or more conditions at the baseline date and 9,368 (7.6%) had 3 or more conditions (prevalent multimorbidity). Overall, we observed a total of 1,334,906 person-years of follow-up; **however, as expected**, the length of follow-up varied by age group. For example, median follow-up was 13.1 years in persons aged 0 to 19 years at baseline, 12.3 years in persons aged 70 to 79 years at baseline, and 4.9 years in persons aged 80 years or older at baseline.

Figure 1 and Supplementary Table C report the incidence of each of the 20 chronic conditions considered separately by age and sex. The incidence of most of the chronic conditions increased steeply with older age. However, the incidence of asthma,

substance abuse disorders, hepatitis, autism spectrum disorder, and infection with human immunodeficiency virus was higher in the younger population compared to persons older than 60 years. The incidence of depression increased from ages 0-19 to 20-39 years, declined from 40-49 to 60-69 years, and increased sharply again thereafter. The incidence of most conditions was higher in men compared to women of the same age; however, women had a higher incidence of depression, arthritis, asthma, and osteoporosis. The incidence curves in men and women crossed at age 50-59 years for cancer and at age 60-69 years for chronic obstructive pulmonary disease (Figure 1).

Incidence of multimorbidity by age, sex, and ethnicity

Figure 2 shows the age-specific incidence rates of multimorbidity in men and women separately (panels A and C), and in three ethnic groups (panels B and D). Both the incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased steeply with older age (Table 1, Table 2, and Figure 2). For example, the incidence of 2 chronic conditions in men was 6.5/1,000 person-years in persons who were ages 0-19 years, and 260.0/1,000 in persons who were ≥ 80 years. The overall incidence of 2 chronic conditions was slightly higher in women compared to men (overall standardized incidence rates 38.8 vs. 35.5/1,000 person-years; Table 1). The incidence of 2 chronic conditions was higher in Blacks compared to Whites, but lower in Asians compared to Whites (see standardized incidence rates in Table 1 and Figure 2). We observed similar patterns for the development of 3 chronic conditions (see standardized incidence rates in Table 2 and Figure 2). The overall incidence of 3 conditions was similar in men

and women (standardized incidence rates 25.5/1,000 person-years in men vs. 26.6/1,000 person-years in women); however, it was higher in Blacks and lower in Asians, compared to Whites (Figure 2).

In the set of sensitivity analyses in which we combined hyperlipidemia and hypertension as a single condition, we observed a slight decrease in the incidence of 2 chronic conditions and of 3 chronic conditions compared with the primary analyses. The overall incidence rate of 2 conditions decreased from 35.0 to 34.0/1,000 person-years in men and from 40.3 to 40.0/1,000 person-years in women. The incidence rate of 3 conditions decreased from 24.7 to 22.5/1,000 person-years in men and from 28.5 to 27.0/1,000 person-years in women (incidence rates non-standardized; data not shown in the Tables). For both 2 and 3 conditions, the decrease in incidence was more sizeable in men than in women.

Incidence of dyads and triads

Table 3 shows the incidence of the most common dyads or triads of chronic conditions in seven age strata and for men and women separately. **As expected,** the incidence of dyads and triads varied extensively with age. For example, the most common incident dyad in persons 0-19 years was depression and asthma (1.8/1,000 person-years in boys or men and 2.9/1,000 person-years in girls or women). By comparison, the most common dyad in persons ≥ 80 years was hypertension and cancer in men (18.9/1,000 person-years) and hypertension and arthritis in women (27.7/1,000 person-years). Similarly, the most common incident triad of conditions in persons aged 0-19 years was depression, asthma, and substance abuse disorders in both sexes. By comparison, the

most common incident triads in persons ≥ 80 years were hypertension, cancer, and arrhythmia in men and hyperlipidemia, hypertension, and arthritis in women.

As expected, the incidence of dyads and triads also varied by sex. In some instances, the composition of the dyads or triads was the same for men and women, but the magnitude of the incidence rate was different. In other instances, the magnitude of the incidence rate was similar in men and women, but the composition of the dyads and triads varied by sex. For example, the most common incident dyad in persons aged 60-69 years was hyperlipidemia and hypertension in both sexes, but the incidence rate was higher in men compared to women (23.4/1,000 person-years vs. 18.8/1,000 person-years). By contrast, the incidence rates of the most common triads in persons aged 60-69 years were similar in men and women (11.6/1,000 vs. 10.3/1,000 person-years); however, they included different conditions (Table 3).

DISCUSSION

Statement of the principal findings

The burden of multimorbidity in the United States is high and is increasing with an aging population and with improvements in survival. We leveraged a unique longitudinal data resource covering an entire, stable, and geographically defined population to examine the incidence of multimorbidity across all ages. The incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased steeply with older age, and the overall risk was similar in men and women. However, the number of people who developed multimorbidity before age 65 was more than four times greater than the number of people who developed multimorbidity after age 65. The incidence of

multimorbidity was highest in Blacks, and lowest in Asians. Finally, **as expected**, the combinations of conditions in incident dyads and triads differed extensively by age and by sex. These results have important implications for identifying individuals at higher risk of developing multimorbidity at different ages. These data are also a first step toward understanding the causes and the consequences of multimorbidity.

Strengths and limitations

A unique strength of our study was the ability to measure the incidence of multimorbidity documented in medical records across seven age groups and for an entire, geographically defined population. We used historical data both to exclude individuals with prevalent multimorbidity at baseline and to follow individuals over a long period of time to accurately document the development of incident multimorbidity. In total, our findings reflect 19 years of data accumulation (5 years before and 14 years after the baseline date).

Unfortunately, there is no standard definition of multimorbidity. Previous studies have included a wide range of chronic conditions and a wide range of time frames. We defined multimorbidity using the 20 conditions selected by US-DHHS which were chosen because they "meet the definition for chronicity, are prevalent [common], and are potentially amenable to public health or clinical interventions or both." [23] However, this definition provides equal weight to each of the 20 conditions without considering the impact of combinations of specific conditions on the quality of life of patients, the complexity of their joint management, and the severity of their long-term outcomes. **In addition, this list does not include a number of conditions that may have a**

significant impact on the burden of multimorbidity in older subjects (e.g., hearing and vision problems). Such conditions should be considered in future studies of multimorbidity. By contrast, the list includes some conditions that were less common in the general population. For example, autism appeared as part of an incident dyad in only 31 persons, and HIV infection in only 41 persons. Therefore, further efforts are needed to refine the list of the most relevant conditions to study multimorbidity, recognizing that the most relevant conditions will vary depending on the age and sex of the population.

Some of the dyads and triads derived by the combination of the 20 conditions selected by the US-DHHS may have a much stronger impact on the complexity of clinical management than others. [27] Therefore, some dyads or triads may be particularly costly for the health system, harder for the patient to manage by themselves, less amenable to a single disease approach to care (e.g., telemonitoring for heart failure), and may have a stronger effect on functionality, severity of symptoms, and risk of death. In addition, social factors (e.g., inadequate insurance, low education) and behavioral factors (e.g., poor diet) not reflected in the list of 20 US-DHHS conditions may be as important, or more important, than the 20 conditions in determining the complexity of clinical management and long-term outcomes. [27]

For example, because hyperlipidemia and hypertension are typically asymptomatic, and are often diagnosed as the result of routine screening, their combination is likely to have a much lower impact on the life of the patient than the combination of schizophrenia and heart failure. However, both combinations are considered multimorbidity by the US-DHHS definition. Our sensitivity analyses highlight

this problem. As expected, when hyperlipidemia and hypertension were considered as a single condition, the overall incidence of multimorbidity decreased. The decreases were relatively small but were more sizeable in men than in women. These findings emphasize the importance of reaching consensus on the list of conditions to be used to define multimorbidity. However, it is difficult to assess the utility of the 20 conditions included in the US-DHHS list without also understanding how different combinations of these conditions impact long term outcomes. Therefore, we plan to continue this initial incidence study with further analyses to assess which combinations of conditions have the greatest impact on adverse outcomes, including patient quality of life and complexity of clinical management. [27]

We defined incident multimorbidity as the date on which a person met the criteria for a second condition or for a third condition. We used an approach similar to that used in the definition for the onset of metabolic syndrome (reaching three of five components of the syndrome). [28,29] This simple operational definition of incident multimorbidity should be easy to replicate, and should facilitate future comparisons with other populations.

Potential limitations of our study include the inability to validate the ICD-9 codes. It was not possible to confirm all diagnoses for the entire study population, and some ICD-9 codes may have been assigned in error (e.g., “rule out” diagnostic codes). To reduce the likelihood of a single ICD-9 code error, we required two or more diagnosis codes separated by more than 30 days for a person to be defined as having a condition. [30] However, if a person received a valid code and was lost to follow-up or died rapidly after diagnosis, we may have underestimated the incidence of some of the conditions.

In addition, we used diagnosis date as a proxy for the true date of onset of the condition.

Some individuals may have moved into Olmsted County after having been diagnosed with one or more chronic conditions elsewhere. If those persons continued to receive care within the REP for a number of years, we captured their chronic condition at the time of subsequent health care visits. However, we did not know the true date of onset for the condition, and the sequence of accumulation of conditions could be distorted. Because the population of Olmsted County is stable, particularly among persons who are 40 years of age or older, [19] we do not expect a major distortion of the multimorbidity incidence rates observed in this study due to migration.

Finally, our study focused on a single geographically defined US population, and the incidence of multimorbidity may differ in other populations. However, the demographic and socioeconomic characteristics of our population are similar to those of the upper Midwest of the United States, [20] and the prevalence of multimorbidity in persons 65 years of age or older was similar in our population compared with the entire US Medicare population. [16] Replication of this study in other populations in the United States and worldwide will allow for useful comparisons. [31]

Comparison with other studies

A number of studies have described the prevalence of multimorbidity in various populations; [1,7-12] however, few studies have described the incidence of multimorbidity, and no incidence studies are available for the US. In 1998, Van den Akker and colleagues estimated the one year incidence of multimorbidity in patients from a

network of family practices in the Netherlands. [32] Incident multimorbidity was defined as the new development of at least 2 of 335 diagnostic categories within a one year period. Overall, 7.9% of their population developed one new disease and 1.3% developed two or more new diseases in one year. The proportion of people who developed two or more new conditions increased with older age, but did not differ substantially by sex. It is difficult to compare our results directly to the Dutch findings because of methodological differences (e.g., number of conditions considered and time frame), and because it is not clear whether some of the participants in the Dutch study already had one or more conditions at baseline. However, we observed similar patterns of increasing incidence with older age, and limited differences between men and women in overall incidence.

More recently, Melis and colleagues assessed the incidence of multimorbidity in Swedish people aged 75 years or older at baseline who participated in a longitudinal cohort study. [33] Incident multimorbidity was defined as the development of at least 2 of 39 chronic conditions during three years of follow-up. Participants with none of the 39 chronic conditions at baseline had a multimorbidity incidence rate of 12.6 per 100 person-years, and patients with one of the 39 conditions at baseline had an incidence rate of 32.9 per 100 person-years. Although we examined fewer conditions than the Swedish group (20 vs. 39), and the ascertainment of incident conditions was different (medical records data vs. survey methods), our incidence rates of multimorbidity in subjects aged 75 years or older were similar (19.1 per 100 person-years in people with no conditions at baseline and 38.9 per 100 person-years in persons with one condition at baseline; both sexes combined; data not shown).

Meaning of the study

To understand the importance of these findings, we draw an analogy with the difference between prevalence and incidence in epidemiologic studies considering one disease at a time. [34,35] Incidence is the direct measure of the risk of people to develop a given disease, whereas prevalence is the percent of people affected by the same disease at one point in time, and reflects both the effect of incidence and the effect of survival after the onset of the disease. [34,35] Similarly, the prevalence of multimorbidity gives us a static picture of the population; however, prevalence may be misleading when studying the mechanisms of multimorbidity. For example, a higher prevalence of multimorbidity in women than in men may be due to a higher risk of women developing multimorbidity, or to a longer survival of women affected by multimorbidity. [16] **Similarly, studying outcomes among persons with prevalent multimorbidity may be clinically relevant, but may not clarify the outcomes of multimorbidity at the population level (e.g., survival bias and inability to study the effect of the duration of multimorbidity).**

Prior studies of the prevalence of multimorbidity have shown a dramatic increase in the number of people living with 2 or more chronic conditions at older ages. [1,7-11] However, the high prevalence of multimorbidity in the older population implies that relatively few older individuals remain at risk of developing multimorbidity. Overall, among persons aged 80 years or older at baseline, only 891 out of 3,710 (24.0%) were at risk of developing 2 chronic conditions (the other 76.0% already had 2 or more of the 20 conditions). Although the persons who reached 80 years of age or older and

remained free of multimorbidity were a particularly resilient group, they had a higher risk of developing subsequent multimorbidity than younger persons.

We also found that the total number of people who developed multimorbidity before age 65 years was more than 4 times greater than the number of people who developed multimorbidity at ages 65 or older (28,378 vs. 6,214). These data emphasize the need to target preventive efforts at much younger ages, but represent only a first step toward future research to identify the social, behavioral, and clinical risk and protective factors for multimorbidity.

We found important differences in the incidence of multimorbidity by ethnicity. The age standardized incidence rates of multimorbidity were higher in Blacks and lower in Asians compared to Whites. Our findings are consistent with previous studies that showed a higher prevalence of multimorbidity in Blacks compared to Whites, but a lower prevalence of multimorbidity in Asians. [8,16,36-38] Our data suggest that some of these differences in prevalence may be attributed to differences in the incidence of the conditions among different ethnic groups. However, differential survival may also contribute to the differences in prevalence. In turn, both differences in incidence and in prevalence may be influenced by socioeconomic factors, lifestyle behaviors, social environment, and healthcare access. Further research is needed to better characterize these disparities and to identify the causal mechanisms that contribute to different development of chronic conditions and to different survival.

As expected, the incidence and the composition of the dyads and triads of conditions varied extensively across age and sex strata. For example, women 20 years of age or older were more likely to have depression as a component of their incident

multimorbidity dyads and triads compared to men. Such differences may lead to different long-term outcomes in men and women. Therefore, these data are useful to understand how multimorbidity develops, and are an important first step toward future research. In particular, such incident data are necessary to study the chronological order of acquisition of multiple chronic conditions in different age, sex, and ethnic strata. Incidence data are also necessary to determine whether the differential order of acquisition is associated with a different risk of adverse long-term outcomes such as hospitalizations, emergency department visits, or death. For example, it is not clear whether acquiring depression prior to arthritis results in worse long-term outcomes compared with acquiring arthritis prior to depression. Future studies are also needed to understand how additional chronic conditions accumulate after the development of a second and third condition. **Finally, the incidence of specific dyads and triads reflects the incidence of the individual conditions in specific age and sex groups. Many of these dyads and triads are expected to develop simply by chance. Therefore, future studies are needed to identify the dyads and triads that co-occur beyond chance. Identification of incident dyads and triads that reflect shared etiologic mechanisms or shared risk factors may lead to combined treatment or prevention strategies.**

Conclusions and clinical implications

It is important and urgent to understand the causes and the consequences of multimordibity to inform efforts to delay and prevent disease onset and to develop effective strategies for caring for patients with multimorbidity. We studied the incidence

of multimorbidity across all ages, separately in men and women, and in three ethnic groups in a geographically defined US population. The incidence of multimorbidity increased steeply with older age and was higher in Blacks but lower in Asians compared to Whites. Men and women had a similar overall risk, but the combinations of conditions within dyads and triads varied extensively by age and by sex. These data represent an important first step toward **identifying conditions which co-occur more frequently than chance alone**, **identifying** specific risk factors for multimorbidity, understanding how chronic conditions accumulate over time, and toward identifying **combinations of conditions that predict** adverse outcomes.

Competing interest declaration:

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have support from any companies for the submitted work; (2) none of the authors have any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have any non-financial interests that may be relevant to the submitted work.

Contributorship statement: Dr. St. Sauver had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor for the study.

Study concept and design: St. Sauver, Boyd, Grossardt, Yawn, Rocca.

Acquisition, analysis, or interpretation of data: St. Sauver, Grossardt, Rocca.

Drafting of the manuscript: St. Sauver, Rocca.

Critical revision of the manuscript for important intellectual content: St. Sauver, Boyd, Grossardt, Bobo, Finney Rutten, Roger, Ebbert, Therneau, Yawn, and Rocca.

Statistical analysis: Grossardt, Therneau.

Obtained funding: Yawn, Rocca.

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Study supervision: Yawn, Rocca.

Identifiable patients: No identifiable patients were included.

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Table 1. Incidence of the second of two chronic conditions (per 1,000 person-years) in persons living in Olmsted County, MN by age, sex, and ethnicity.

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
All ethnic groups						
0-19	18,879	140,653	6.5 (921)	18,024	134,725	8.5 (1,151)
20-39	27,732	151,734	17.2 (2,613)	28,571	158,252	25.1 (3,972)
40-49	16,396	82,324	43.6 (3,590)	16,713	85,660	45.8 (3,920)
50-59	11,779	52,085	85.2 (4,436)	12,398	55,270	84.6 (4,674)
60-69	5,218	19,653	139.4 (2,739)	5,603	21,246	135.3 (2,874)
70-79	1,775	5,451	209.9 (1,144)	2,184	6,660	202.0 (1,345)
≥ 80	531	1,589	260.0 (413)	1,016	2,887	277.1 (800)
0-64	50,648	439,254	29.7 (13,059)	51,056	447,399	34.2 (15,319)
≥ 65	3,794	14,236	196.5 (2,797)	4,636	17,300	197.5 (3,417)
All ages	52,479	453,489	35.0 (15,856)	53,582	464,699	40.3 (18,736)
Standardized†	---	---	35.5	---	---	38.8
Blacks						
0-19	877	6,411	5.5 (35)	749	5,362	6.0 (32)
20-39	1,099	6,178	16.5 (102)	934	5,647	23.0 (130)
40-49	429	1,836	63.2 (116)	324	1,392	61.8 (86)
50-59	180	683	105.3 (72)	139	513	121.0 (62)
60-69	60	223	134.8 (30)	47	150	193.2 (29)
70-79	18	71	140.1 (10)	23	60	200.4 (12)
≥ 80	4	11	274.0 (3)	3	5	580.3 (3)
0-64	1,848	15,240	22.0 (335)	1,563	13,010	25.5 (332)
≥ 65	48	173	190.8 (33)	37	118	185.7 (22)
All ages	1,873	15,413	23.9 (368)	1,587	13,128	27.0 (354)
Standardized†	---	---	38.9	---	---	48.5
Asians						
0-19	818	6,331	3.5 (22)	826	6,299	5.6 (35)
20-39	1,090	6,372	15.1 (96)	1,168	7,167	14.6 (105)
40-49	534	2,464	39.8 (98)	591	2,869	33.8 (97)
50-59	339	1,588	71.8 (114)	376	1,687	79.4 (134)
60-69	159	592	120.0 (71)	185	570	161.3 (92)
70-79	51	163	140.8 (23)	74	177	271.6 (48)
≥ 80	21	60	216.6 (13)	40	92	358.1 (33)
0-64	1,897	17,137	21.6 (370)	1,997	18,399	23.3 (429)
≥ 65	114	433	154.7 (67)	159	463	248.4 (115)
All ages	1,954	17,571	24.9 (437)	2,105	18,862	28.8 (544)
Standardized†	---	---	29.5	---	---	34.9
Whites						
0-19	14,956	119,686	6.8 (818)	14,414	114,906	9.0 (1,032)
20-39	21,792	128,801	17.9 (2,303)	23,214	135,903	26.5 (3,599)
40-49	14,426	74,921	43.6 (3,269)	15,088	79,123	46.1 (3,646)
50-59	10,795	48,361	85.8 (4,149)	11,520	51,901	84.8 (4,399)

Table 1. Continued

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
60-69	4,823	18,362	140.4 (2,578)	5,221	20,075	134.7 (2,704)
70-79	1,653	5,090	212.6 (1,082)	2,030	6,301	200.9 (1,266)
≥ 80	497	1,495	262.8 (393)	953	2,754	274.5 (756)
0-64	40,703	383,410	31.2 (11,952)	42,149	394,566	35.9 (14,170)
≥ 65	3,517	13,306	198.4 (2,640)	4,317	16,398	197.1 (3,232)
All ages	42,382	396,716	36.8 (14,592)	44,465	410,964	42.3 (17,402)
Standardized†	---	---	36.0	---	---	39.4

* Incidence rates are reported per 1,000 person-years.
† Incidence rates were directly standardized to the total US population from the 2010 US Decennial Census after removing the number of people with prevalent multimorbidity (≥ 2 chronic conditions) as projected from our previous study (see Supplementary Table B).[16]

Table 2. Incidence of the third of three chronic conditions (per 1,000 person-years) in persons living in Olmsted County, MN by age, sex, and ethnicity.

	Men			Women		
Ethnicity age (years)	**Persons**	**Person-years**	**Incidence rate* (n)**	**Persons**	**Person-years**	**Incidence rate* (n)**
All ethnic groups						
0-19	19,029	144,025	1.3 (186)	18,203	138,055	2.0 (282)
20-39	28,721	162,693	6.9 (1,123)	30,135	177,878	10.9 (1,944)
40-49	17,901	95,582	22.6 (2,157)	18,824	103,400	24.2 (2,507)
50-59	14,398	69,907	52.8 (3,688)	15,475	76,247	51.5 (3,930)
60-69	7,517	31,617	99.5 (3,146)	8,313	35,342	96.7 (3,416)
70-79	3,109	10,639	169.7 (1,805)	3,899	13,653	156.4 (2,136)
≥ 80	992	3,230	218.9 (707)	1,970	6,414	230.6 (1,479)
0-64	53,073	491,536	18.0 (8,852)	54,280	517,164	20.2 (10,432)
≥ 65	5,938	26,156	151.4 (3,960)	7,706	33,825	155.6 (5,262)
All ages	55,898	517,693	24.7 (12,812)	58,450	550,989	28.5 (15,694)
Standardized†	---	---	25.5	---	---	26.6
Blacks						
0-19	879	6,530	1.1 (7)	751	5,458	1.1 (6)
20-39	1,123	6,428	8.6 (55)	960	6,032	9.4 (57)
40-49	460	2,126	34.8 (74)	373	1,723	41.2 (71)
50-59	218	952	69.3 (66)	173	737	69.2 (51)
60-69	81	312	96.1 (30)	70	241	132.8 (32)
70-79	27	108	129.4 (14)	28	84	191.0 (16)
≥ 80	5	23	172.3 (4)	5	9	321.2 (3)
0-64	1,883	16,227	13.3 (216)	1,602	14,101	14.5 (205)
≥ 65	58	252	135.1 (34)	54	183	169.2 (31)
All ages	1,911	16,479	15.2 (250)	1,633	14,284	16.5 (236)
Standardized†	---	---	28.2	---	---	34.8
Asians						
0-19	823	6,419	0.6 (4)	832	6,442	1.6 (10)
20-39	1,109	6,747	6.2 (42)	1,206	7,587	4.6 (35)
40-49	574	2,841	18.7 (53)	651	3,327	20.7 (69)
50-59	390	1,942	44.8 (87)	439	2,191	46.1 (101)
60-69	203	830	78.3 (65)	254	966	97.3 (94)
70-79	80	259	138.8 (36)	110	353	141.5 (50)
≥ 80	32	84	202.0 (17)	84	228	241.2 (55)
0-64	1,940	18,472	12.2 (225)	2,074	20,167	12.9 (261)
≥ 65	165	650	121.5 (79)	258	929	164.7 (153)
All ages	2,027	19,122	15.9 (304)	2,235	21,096	19.6 (414)
Standardized†	---	---	21.1	---	---	23.2
Whites						
0-19	15,088	122,717	1.3 (160)	14,576	117,885	2.2 (259)
20-39	22,681	138,725	7.1 (990)	24,638	154,160	11.7 (1,799)
40-49	15,811	87,199	22.7 (1,978)	17,025	95,693	24.1 (2,308)
50-59	13,262	65,243	53.1 (3,464)	14,443	71,770	51.7 (3,714)

Table 2. Continued

Ethnicity age (years)	Men			Women		
	Persons	Person-years	Incidence rate* (n)	Persons	Person-years	Incidence rate* (n)
60-69	7,028	29,816	100.8 (3,005)	7,796	33,477	96.9 (3,244)
70-79	2,930	10,061	171.9 (1,729)	3,680	13,006	157.2 (2,045)
≥ 80	942	3,093	219.5 (679)	1,848	6,105	231.0 (1,410)
0-64	42,953	432,089	19.0 (8,213)	45,157	459,919	21.2 (9,761)
≥ 65	5,572	24,764	153.1 (3,792)	7,224	32,177	155.9 (5,018)
All ages	45,583	456,853	26.3 (12,005)	49,033	492,097	30.0 (14,779)
Standardized†	---	---	25.7	---	---	27.0

* Incidence rates are reported per 1,000 person-years.
† Incidence rates were directly standardized to the total US population from the 2010 US Decennial Census after removing the number of people with prevalent multimorbidity (≥ 3 chronic conditions) as projected from our previous study (see Supplementary Table B).[16]

Table 3. Incidence rates (per 1,000 person-years) and composition of the most common dyads and triads of chronic conditions in persons living in Olmsted County, MN by age and sex.

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
0 – 19								
1	DEP - AST	1.8 (257)	DEP - AST	2.9 (395)	DEP - AST - SUB	0.4 (53)	DEP - AST - SUB	0.4 (62)
2	DEP - SUB	1.3 (178)	DEP - SUB	1.8 (240)	DEP - AST - COPD	0.1 (17)	DEP - AST - COPD	0.3 (39)
3	AST - COPD	0.9 (122)	AST - COPD	0.7 (91)	DEP - SUB - SZO	0.1 (8)	DEP - ARR - AST	0.2 (27)
4	AST - SUB	0.4 (56)	DEP - ARR	0.4 (50)	LIP - DEP - AST	<0.1 (7)	DEP - ARR - SUB	0.1 (13)
5	DEP - ARR	0.1 (21)	DEP - COPD	0.4 (48)	3-way tie ‖	< 0.1 (6)	DEP - SUB - COPD	0.1 (12)
20 – 39								
1	DEP - SUB	3.5 (525)	DEP - AST	3.4 (531)	DEP - AST - SUB	0.4 (73)	DEP - AST - SUB	0.8 (134)
2	LIP - HTN	1.4 (207)	DEP - SUB	2.9 (463)	DEP - SUB - SZO	0.4 (69)	DEP - AST - COPD	0.7 (121)
3	DEP - AST	1.1 (174)	DEP - CAN	2.0 (309)	LIP - HTN - DIA	0.4 (65)	DEP - ARR - AST	0.4 (77)
4	LIP - DEP	1.0 (155)	LIP - DEP	1.7 (267)	DEP - ARR - SUB	0.3 (46)	DEP - SUB - COPD	0.3 (61)
5	LIP - DIA	0.9 (137)	DEP - ARR	1.4 (222)	LIP - HTN - DEP	0.3 (45)	LIP - DEP - AST	0.3 (58)
40 – 49								
1	LIP - HTN	7.0 (580)	LIP - DEP	4.1 (354)	LIP - HTN - DIA	3.1 (294)	LIP - HTN - DIA	1.4 (147)
2	LIP - DIA	4.4 (363)	LIP - HTN	3.6 (308)	LIP - HTN - DEP	1.2 (115)	LIP - HTN - DEP	1.1 (114)
3	LIP - DEP	3.5 (285)	DEP - ART	2.6 (224)	LIP - HTN - ART	0.9 (84)	LIP - DEP - DIA	1.0 (99)
4	LIP - ART	2.4 (198)	DEP - CAN	2.6 (224)	LIP - HTN - CAD	0.9 (83)	LIP - DEP - ART	0.8 (84)
5	DEP - SUB	1.9 (157)	HTN - DEP	2.4 (203)	LIP - DEP - DIA	0.8 (74)	LIP - DEP - AST	0.6 (63)
50 – 59								
1	LIP - HTN	14.5 (757)	LIP - HTN	9.8 (540)	LIP - HTN - DIA	7.2 (504)	LIP - HTN - DIA	3.9 (300)
2	LIP - DIA	8.7 (455)	LIP - ART	6.5 (359)	LIP - HTN - ART	3.5 (242)	LIP - HTN - ART	3.0 (232)
3	LIP - ART	6.7 (351)	LIP - DEP	5.9 (325)	LIP - HTN - CAD	3.0 (208)	LIP - HTN - DEP	2.4 (185)
4	LIP - CAN	4.6 (241)	DEP - ART	4.8 (265)	LIP - HTN - DEP	1.9 (131)	LIP - DEP - ART	2.4 (180)
5	HTN - DIA	4.4 (227)	LIP - CAN	4.5 (246)	LIP - HTN - ARR	1.7 (117)	LIP - HTN - CAN	1.8 (136)

Table 3. Continued 1

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
60 – 69								
1	LIP - HTN	23.4 (460)	LIP - HTN	18.8 (400)	LIP - HTN - DIA	11.6 (366)	LIP - HTN - ART	10.3 (363)
2	LIP - DIA	11.5 (226)	LIP - ART	15.5 (330)	LIP - HTN - ART	6.8 (214)	LIP - HTN - DIA	7.4 (263)
3	LIP - ART	11.4 (224)	HTN - ART	10.4 (220)	LIP - HTN - CAD	6.3 (200)	LIP - HTN - CAN	4.6 (164)
4	LIP - CAN	10.0 (196)	LIP - CAN	6.8 (145)	LIP - HTN - CAN	4.9 (155)	LIP - ART - CAN	2.9 (102)
5	HTN - DIA	8.6 (169)	LIP - DIA	6.4 (135)	LIP - HTN - ARR	3.4 (106)	LIP - DIA - ART	2.7 (95)
6	HTN - ART	7.7 (152)	ART - CAN	4.9 (105)	LIP - DIA - ART	2.9 (91)	LIP - HTN - DEP	2.6 (93)
7	LIP - CAD	6.9 (136)	LIP - OST	4.9 (105)	LIP - ART - CAN	2.6 (82)	LIP - DEP - ART	2.5 (89)
8	HTN - CAN	6.2 (121)	HTN - CAN	4.8 (103)	LIP - DIA - CAD	2.4 (76)	LIP - ART - ARR	2.3 (83)
9	ART - CAN	4.5 (89)	HTN - DIA	4.6 (97)	HTN - DIA - ART	2.2 (71)	LIP - HTN - OST	2.2 (79)
10	LIP - ARR	4.5 (88)	LIP - DEP	4.4 (94)	LIP - ARR - CAD	2.2 (68)	HTN - DIA - ART	2.2 (77)
70 – 79								
1	LIP - HTN	19.1 (104)	LIP - HTN	26.0 (173)	LIP - HTN - CAN	11.9 (127)	LIP - HTN - ART	15.7 (214)
2	HTN - CAN	18.9 (103)	HTN - ART	18.5 (123)	LIP - HTN - DIA	10.4 (111)	LIP - HTN - DIA	9.8 (134)
3	LIP - CAN	15.0 (82)	LIP - ART	15.5 (103)	LIP - HTN - CAD	9.7 (103)	LIP - HTN - CAN	6.0 (82)
4	HTN - ART	13.2 (72)	LIP - OST	9.0 (60)	LIP - HTN - ART	9.4 (100)	LIP - ART - CAN	5.4 (74)
5	ART - CAN	11.6 (63)	HTN - CAN	8.9 (59)	LIP - HTN - ARR	5.5 (58)	HTN - ART - CAN	5.2 (71)
6	LIP - ART	11.6 (63)	HTN - OST	8.3 (55)	HTN - ART - CAN	4.9 (52)	LIP - ART - OST	5.2 (71)
7	HTN - DIA	10.1 (55)	ART - CAN	8.1 (54)	LIP - ART - CAN	4.7 (50)	LIP - HTN - OST	4.6 (63)
8	HTN - ARR	9.9 (54)	ART - OST	7.8 (52)	HTN - CAN - ARR	4.2 (45)	LIP - HTN - ARR	4.5 (62)
9	LIP - CAD	7.7 (42)	HTN - DIA	7.8 (52)	HTN - ART - ARR	4.1 (44)	HTN - ART - OST	4.0 (55)
10	LIP - DIA	7.7 (42)	LIP - CAN	7.8 (52)	LIP - DIA - CAN	4.1 (44)	2-way tie ¶	3.4 (47)
≥ 80								
1	HTN - CAN	18.9 (30)	HTN - ART	27.7 (80)	HTN - CAN - ARR	8.7 (28)	LIP - HTN - ART	10.3 (66)
2	HTN - ARR	17.6 (28)	LIP - HTN	23.2 (67)	LIP - HTN - CAN	7.7 (25)	HTN - ART - OST	9.8 (63)
3	HTN - ART	14.5 (23)	HTN - ARR	17.7 (51)	HTN - ART - CAN	7.4 (24)	HTN - ART - CAN	9.2 (59)

Table 3. Continued 2

Age (years) Rank *	Dyad				Triad			
	Men		Women		Men		Women	
	Combination †	Rate (n) ‡	Combination †	Rate (n) ‡	Combination †	Rate (n) §	Combination †	Rate (n) §
4	ART - ARR	12.0 (19)	HTN - CAN	15.2 (44)	LIP - HTN - ART	6.2 (20)	HTN - ART - ARR	9.0 (58)
5	CAN - ARR	12.0 (19)	HTN - OST	14.9 (43)	LIP - HTN - ARR	5.9 (19)	LIP - HTN - OST	5.9 (38)
6	HTN - CAD	10.1 (16)	HTN - DEM	11.8 (34)	ART - CAN - ARR	5.3 (17)	LIP - HTN - DIA	5.0 (32)
7	LIP - HTN	10.1 (16)	ART - CAN	10.0 (29)	HTN - ART - ARR	5.3 (17)	LIP - HTN - ARR	4.7 (30)
8	ART - CAN	8.8 (14)	ART - OST	9.7 (28)	HTN - CAN - CAD	5.0 (16)	LIP - HTN - CAN	4.5 (29)
9	CAN - CAD	8.8 (14)	HTN - CKD	7.6 (22)	LIP - HTN - CAD	5.0 (16)	ART - CAN - OST	4.4 (28)
10	HTN - DEM	8.8 (14)	3-way tie **	7.3 (21)	LIP - ART - CAN	4.6 (15)	LIP - HTN - CAD	3.9 (25)

* Rank order from the most frequent to the least frequent incident dyad or triad. For the younger age groups (through age 59 years), we reported the 5 most frequent incident combinations; for the older age groups (60 years and older), we reported the 10 most frequent incident combinations.

† Definition of acronyms in order of frequency: LIP = hyperlipidemia; HTN = hypertension; DEP = depression; DIA = diabetes; ART = arthritis; CAN = cancer; ARR = cardiac arrhythmias; AST = asthma; CAD = coronary artery disease; SUB = substance abuse disorders; COPD = chronic obstructive pulmonary disease; OST = osteoporosis; CKD = chronic kidney disease; STR = stroke; CHF = congestive heart failure; DEM = dementia; SZO = schizophrenia; HEP = hepatitis; AUT = autism spectrum disorder; and HIV = human immunodeficiency virus.

‡ Incidence rates per 1,000 person years. Rates can be calculated by dividing the number of incident persons in parentheses by the person- years at risk of 2 conditions from each age- and sex-specific stratum for all ethnic groups combined in Table 1.

§ Incidence rates per 1,000 person years. Rates can be calculated by dividing the number of incident persons in parentheses by the person-years at risk of 3 conditions from each age- and sex-specific stratum for all ethnic groups combined in Table 2.

‖ Three-way tie for the rank 5 triad in men ages 0-19 years: 1) AST-SUB-COPD; 2) DEP-ARR-SUB; 3) DEP-AST-DEM.

¶ Two-way tie for the rank 10 triad in women ages 70-79 years: 1) HTN-ART-ARR; 2) LIP-CAN-OST.

** Three-way tie for the rank 10 dyad in women ages ≥ 80 years: 1) ART-ARR; 2) HTN-DIA; 3) LIP-ART.

Figure Legends

Figure 1. Age- and sex-specific incidence rates (per 1,000 person-years) of the 20 chronic conditions considered separately. The 20 panels are presented by rows in decreasing order of frequency (by overall age- and sex-standardized prevalence). [16]

Figure 2. Incidence rates (per 1,000 person-years) of 2 chronic conditions (second condition in a dyad) and of 3 chronic conditions (third condition in a triad) in men and women separately (panels A and C), and stratified by ethnicity (panels B and D).

Figure 1

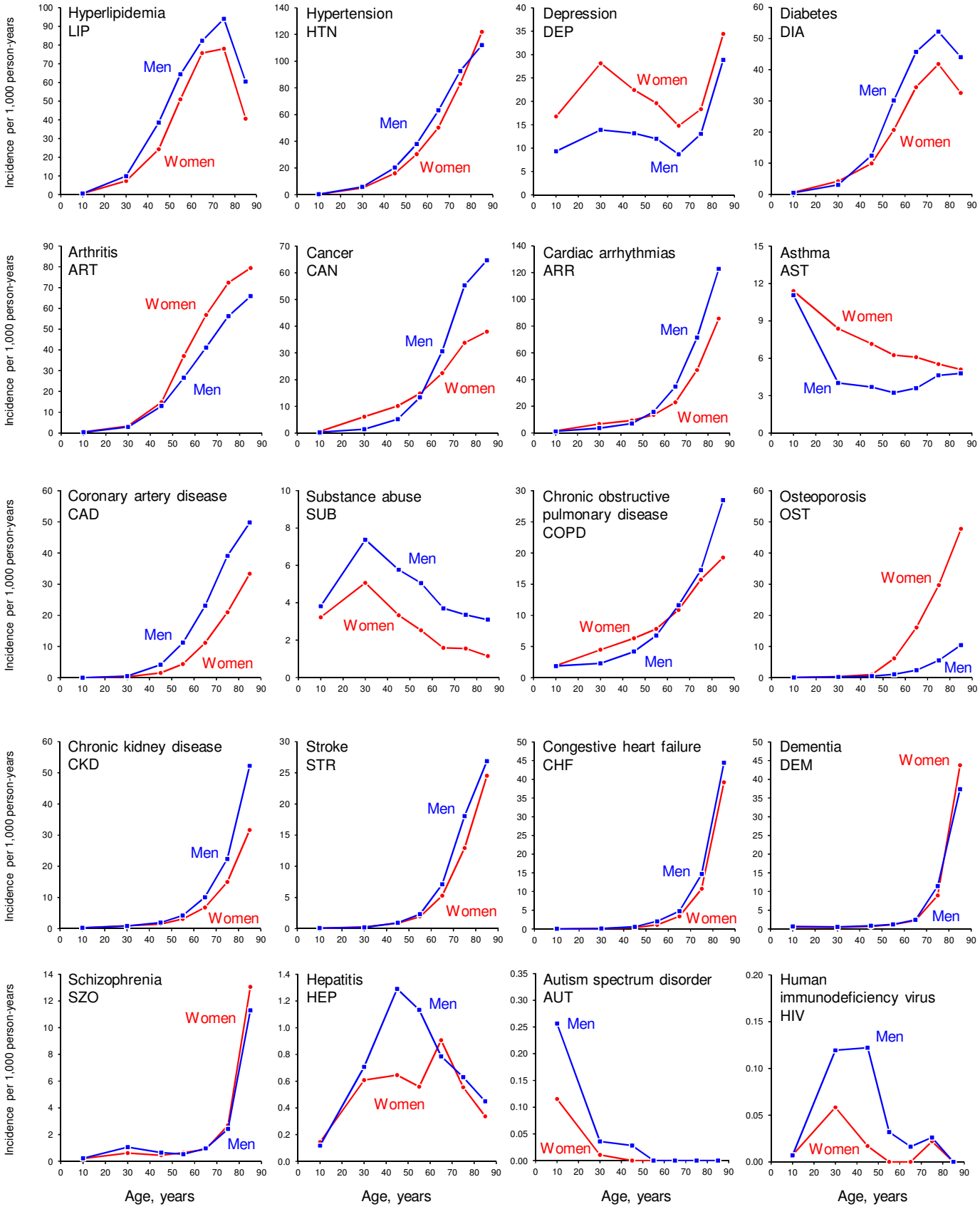
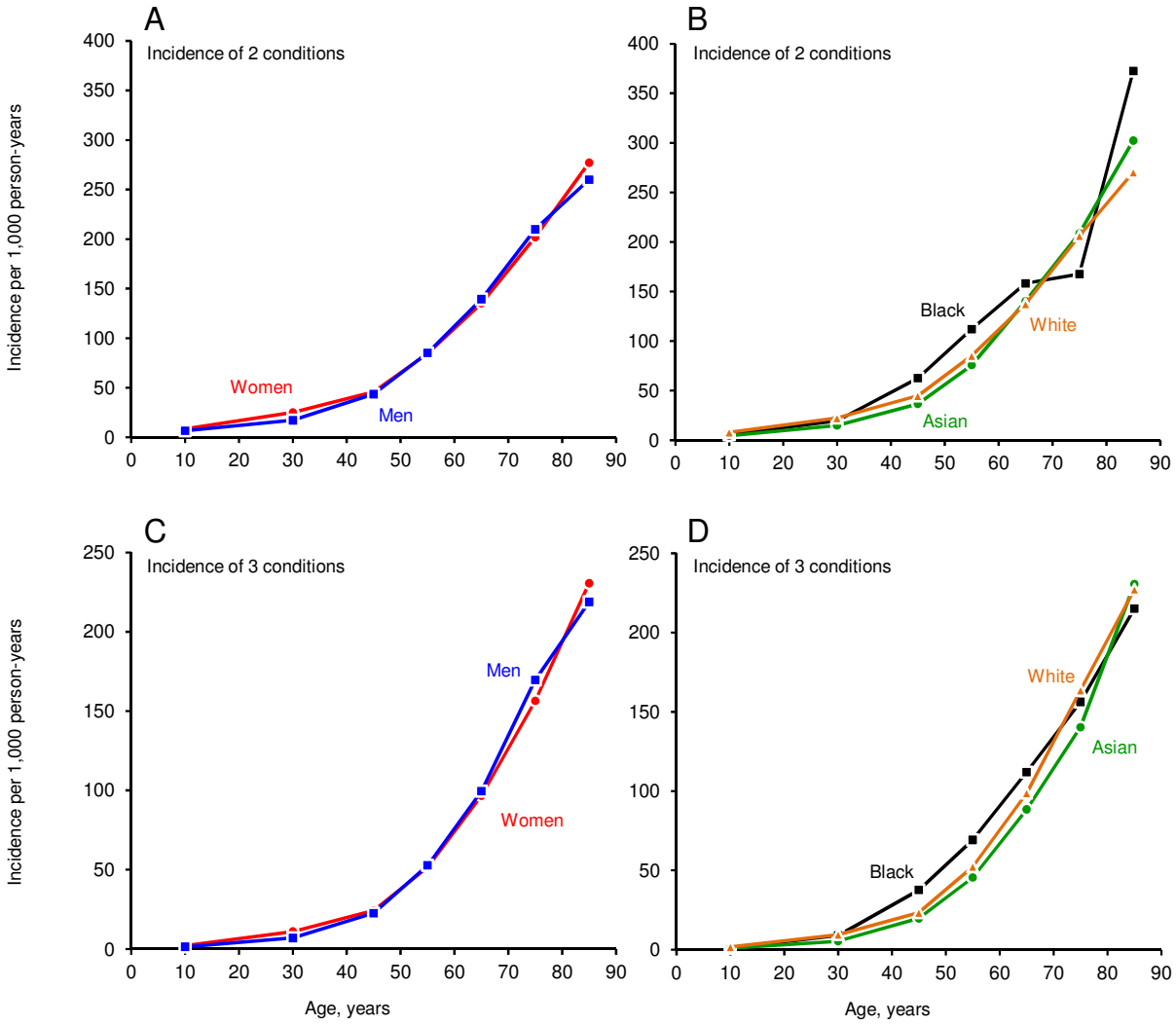

Hyperlipidemia
LIP
Hypertension
HTN
Depression
DEP
Diabetes
DIA
Arthritis
ART
Cancer
CAN
Cardiac arrhythmias
ARR
Asthma
AST
Coronary artery disease
CAD
Substance abuse
SUB
Chronic obstructive pulmonary disease
COPD
Osteoporosis
OST
Chronic kidney disease
CKD
Stroke
STR
Congestive heart failure
CHF
Dementia
DEM
Schizophrenia
SZO
Hepatitis
HEP
Autism spectrum disorder
AUT
Human immunodeficiency virus
HIV
Men
Women
Incidence per 1,000 person-years
Age, years

Figure 2



Appendix 1: Supplementary tables A-C [posted as supplied by the authors]

Supplementary table A. List of the twenty chronic conditions selected by the US-DHHS *

Description †	Acronym or Abbreviation	CCC ‡	CMS (ICD-9 codes) §
Hyperlipidemia	LIP	53	272.0, 272.1, 272.2, 272.3, 272.4
Hypertension	HTN	98, 99	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 362.11, 437.2
Depression	DEP	657	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	DIA	49,50	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
Arthritis	ART	202, 203	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91
Cancer	CAN	11-43	Female breast cancer: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3. Colorectal cancer: 154.0, 154.1, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 230.3, 230.4, V10.05. Prostate cancer: 185, 233.4, V10.46. Lung cancer: 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11.
Cardiac arrhythmias	ARR	105-106	427.31
Asthma	AST	128	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Coronary artery disease	CAD	100, 101	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.8, 414.9

Supplementary table A. List of the twenty chronic conditions selected by the US-DHHS * (continued)

Description †	Acronym or Abbreviation	CCC ‡	CMS (ICD-9 codes) §
Substance abuse disorders (drug and alcohol)	SUB	660-661	Not applicable
Chronic obstructive pulmonary disease	COPD	127	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496
Osteoporosis	OST	206	733.00, 733.01, 733.02, 733.03, 733.09
Chronic kidney disease	CKD	158	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Stroke	STR	109-112	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01,434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Congestive heart failure	CHF	108	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Dementia (including Alzheimer's and other senile dementias)	DEM	653	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.8, 797
Schizophrenia	SZO	659	Not applicable
Hepatitis	HEP	6	Not applicable
Autism spectrum disorder	AUT	299.00, 299.01 ‖	Not applicable
Human immunodeficiency virus (HIV)	HIV	5	Not applicable

* CCC = Clinical Classification Codes; CMS = Centers for Medicare and Medicaid Services; ICD-9 = International Classification of Diseases, 9th revision; US-DHHS = US Department of Health and Human Services.

† The 20 conditions were defined by the US-DHHS as detailed elsewhere. (Goodman et al., 2013) Each condition is defined by having a code in either the CCC group of codes or the CMS group of codes. Conditions are listed in decreasing order of frequency (by overall age and sex standardized prevalence; same order as in Figure 1).

‡ We list the CCC chapters developed by the Agency for Healthcare Research and Quality (AHRQ). Each CCC chapter includes a list of ICD-9 codes as detailed elsewhere. (Cohen et al., 2009)

§ We list the ICD-9 codes defined in the Chronic Conditions Data Warehouse of the CMS.

‖ Autism-spectrum disorder is not defined in either the CCC or the CMS code groupings, but rather is defined by two distinct ICD-9 codes.

Supplementary table B. Total US population used for direct standardization of incidence rates

Age	Men			Women			Adjusting population §
	US Total (n) *	Prev. % †	At risk (n) ‡	US Total (n) *	Prev. % †	At risk (n) ‡	
Prevalence of 2 chronic conditions							
0-19 y	42,592	1.26	42,054	40,675	1.40	40,108	82,162
20-39 y	41,688	6.98	38,779	41,140	8.74	37,546	76,325
40-49 y	21,603	20.37	17,202	21,995	19.71	17,660	34,862
50-59 y	20,456	38.13	12,657	21,505	35.77	13,813	26,470
60-69 y	13,930	59.41	5,654	15,323	58.35	6,381	12,036
70-79 y	7,427	79.73	1,506	9,170	78.27	1,993	3,498
≥ 80 y	4,084	87.86	496	7,152	86.41	972	1,467
Prevalence of 3 chronic conditions							
0-19 y	42,592	0.17	42,521	40,675	0.25	40,575	83,096
20-39 y	41,688	2.12	40,805	41,140	2.57	40,083	80,887
40-49 y	21,603	9.40	19,572	21,995	8.55	20,115	39,687
50-59 y	20,456	21.06	16,148	21,505	19.30	17,355	33,503
60-69 y	13,930	40.88	8,235	15,323	38.32	9,452	17,687
70-79 y	7,427	65.11	2,591	9,170	62.05	3,480	6,071
≥ 80 y	4,084	78.93	861	7,152	74.17	1,848	2,708

* Population (in thousands) of the entire United States from the decennial census of 2010.
† Prevalence of 2 or 3 chronic conditions from our previous study in Olmsted County, MN. (Rocca et., al, In Press)
‡ Total population at risk (in thousands) after removing the estimated prevalent persons who have already reached 2 or 3 chronic conditions.
§ The total population (in thousands) used in Tables 1 and 2 for direct standardization.

Supplementary table C. Incidence of twenty chronic conditions considered individually

Condition age (years)	Men Persons	Men Person-years	Men Incidence rate * (n)	Women Persons	Women Person-years	Women Incidence rate * (n)
Hyperlipidemia						
0-19	18,996	143,882	0.6 (91)	18,174	138,140	0.7 (94)
20-39	28,437	159,373	10.0 (1,586)	30,040	179,745	7.3 (1,311)
40-49	16,512	82,705	38.5 (3,186)	18,328	99,834	24.3 (2,428)
50-59	11,993	54,436	64.4 (3,504)	14,248	68,637	51.0 (3,500)
60-69	6,023	25,216	82.4 (2,077)	7,111	30,967	75.7 (2,345)
70-79	3,077	11,661	94.1 (1,097)	3,821	14,970	78.0 (1,168)
≥ 80	1,712	7,163	60.5 (433)	3,319	15,777	40.6 (641)
Hypertension						
0-19	19,029	144,237	0.5 (65)	18,215	138,569	0.4 (51)
20-39	28,626	162,582	5.9 (954)	30,315	183,220	5.0 (908)
40-49	17,289	92,372	20.4 (1,882)	18,790	105,079	16.0 (1,683)
50-59	13,481	67,250	38.0 (2,556)	15,013	77,172	30.3 (2,341)
60-69	7,077	31,540	63.2 (1,993)	7,971	36,990	50.3 (1,859)
70-79	3,331	13,402	92.6 (1,241)	3,941	16,136	83.0 (1,339)
≥ 80	1,354	5,198	112.0 (582)	2,053	7,919	121.9 (965)
Depression						
0-19	18,794	139,315	9.3 (1,297)	17,774	131,126	16.8 (2,198)
20-39	27,342	150,493	13.9 (2,091)	27,026	146,257	28.2 (4,118)
40-49	17,234	94,033	13.2 (1,238)	16,533	89,742	22.4 (2,013)
50-59	15,027	81,059	12.0 (974)	14,642	77,962	19.6 (1,530)
60-69	10,174	54,355	8.7 (472)	10,229	54,471	14.8 (805)
70-79	6,720	34,274	13.0 (447)	7,408	37,536	18.3 (688)
≥ 80	3,482	17,009	28.9 (491)	5,313	28,290	34.4 (974)
Diabetes						
0-19	19,025	144,155	0.5 (68)	18,190	138,186	0.7 (90)
20-39	28,799	165,115	3.0 (503)	30,406	184,616	4.2 (775)
40-49	18,193	100,104	12.4 (1,246)	19,617	112,231	9.9 (1,112)
50-59	15,419	80,259	30.1 (2,417)	17,181	92,695	20.7 (1,917)
60-69	9,394	45,589	45.7 (2,084)	10,854	55,408	34.4 (1,906)
70-79	5,427	25,396	52.2 (1,326)	6,966	33,383	41.8 (1,395)
≥ 80	2,840	13,550	44.1 (597)	5,074	26,909	32.6 (876)
Arthritis						
0-19	19,032	144,320	0.3 (49)	18,205	138,450	0.5 (68)
20-39	28,827	165,354	2.9 (477)	30,425	185,391	3.4 (625)
40-49	18,202	99,821	13.0 (1,298)	19,464	109,658	14.8 (1,628)
50-59	15,324	79,753	26.6 (2,120)	16,304	83,158	37.0 (3,079)
60-69	9,295	45,576	41.1 (1,874)	9,227	43,244	56.8 (2,458)
70-79	5,193	23,106	56.3 (1,300)	5,185	22,090	72.3 (1,598)
≥ 80	2,317	9,836	65.9 (648)	3,252	14,434	79.4 (1,146)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 1)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Cancer						
0-19	19,020	144,181	0.3 (40)	18,180	138,347	0.6 (84)
20-39	28,832	166,077	1.5 (241)	29,734	176,247	6.1 (1,079)
40-49	18,402	103,035	5.2 (534)	18,658	105,898	10.1 (1,072)
50-59	15,899	85,763	13.4 (1,145)	16,361	89,149	14.8 (1,321)
60-69	9,821	49,157	30.7 (1,507)	10,480	54,117	22.5 (1,215)
70-79	5,146	23,169	55.3 (1,281)	6,552	31,563	33.7 (1,065)
≥ 80	2,112	9,137	64.7 (591)	4,411	21,933	38.0 (833)
Cardiac arrhythmias						
0-19	19,008	143,802	1.2 (170)	18,203	137,966	1.7 (228)
20-39	28,736	164,530	3.6 (590)	30,250	181,665	6.7 (1,216)
40-49	18,324	102,268	7.1 (722)	19,444	110,842	9.3 (1,036)
50-59	15,939	85,675	15.8 (1,354)	17,211	94,404	13.5 (1,274)
60-69	10,068	50,190	34.7 (1,741)	11,262	58,346	22.9 (1,337)
70-79	5,514	24,370	71.4 (1,741)	7,095	33,211	47.1 (1,563)
≥ 80	2,193	8,604	122.9 (1,057)	4,365	20,213	85.6 (1,731)
Asthma						
0-19	17,856	126,216	11.1 (1,395)	17,443	125,314	11.4 (1,428)
20-39	27,126	155,022	4.0 (624)	28,383	168,182	8.4 (1,409)
40-49	18,102	101,654	3.7 (376)	18,845	107,595	7.2 (770)
50-59	16,129	89,329	3.2 (289)	16,920	94,186	6.3 (589)
60-69	10,930	58,658	3.6 (211)	11,535	62,226	6.1 (379)
70-79	7,051	36,059	4.6 (167)	7,987	41,216	5.5 (228)
≥ 80	3,741	18,815	4.8 (90)	5,878	32,584	5.1 (166)
Coronary artery disease						
0-19	19,050	144,593	0.0 (0)	18,227	138,785	0.0 (0)
20-39	28,982	167,484	0.5 (79)	30,647	188,499	0.3 (50)
40-49	18,565	104,424	4.1 (432)	20,213	117,920	1.5 (177)
50-59	15,875	85,866	11.2 (963)	18,177	101,860	4.4 (446)
60-69	9,540	47,996	23.1 (1,108)	11,891	62,970	11.2 (703)
70-79	5,081	23,713	39.1 (927)	7,473	37,099	21.0 (779)
≥ 80	2,213	10,046	49.8 (500)	4,868	25,325	33.4 (845)
Substance abuse disorders						
0-19	18,850	142,916	3.8 (545)	18,083	137,309	3.2 (443)
20-39	28,004	157,109	7.4 (1,159)	29,846	179,474	5.1 (910)
40-49	18,038	100,943	5.8 (582)	19,722	114,415	3.3 (381)
50-59	16,085	89,151	5.1 (451)	18,013	101,745	2.5 (257)
60-69	11,001	59,373	3.7 (220)	12,398	67,817	1.6 (108)
70-79	7,194	37,259	3.4 (125)	8,599	44,899	1.6 (70)
≥ 80	3,882	19,697	3.1 (61)	6,325	35,542	1.2 (41)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 2)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Chronic obstructive pulmonary disease						
0-19	18,973	142,682	1.9 (267)	18,140	136,992	1.9 (263)
20-39	28,674	164,415	2.3 (376)	30,052	181,106	4.5 (811)
40-49	18,348	103,031	4.2 (430)	19,432	111,533	6.3 (704)
50-59	16,170	88,965	6.7 (600)	17,425	96,719	7.8 (756)
60-69	10,615	55,796	11.6 (648)	11,556	61,640	10.9 (670)
70-79	6,439	32,418	17.2 (559)	7,661	38,688	15.7 (608)
≥ 80	3,234	15,771	28.5 (449)	5,397	29,472	19.3 (568)
Osteoporosis						
0-19	19,048	144,579	<0.1 (5)	18,226	138,759	<0.1 (5)
20-39	28,982	167,571	0.2 (41)	30,631	188,380	0.3 (58)
40-49	18,740	106,337	0.5 (53)	20,191	117,986	1.0 (119)
50-59	16,745	93,377	1.1 (99)	18,194	101,448	6.2 (628)
60-69	11,326	60,849	2.4 (144)	11,750	61,299	16.1 (987)
70-79	7,280	37,236	5.5 (206)	7,330	34,844	29.7 (1,034)
≥ 80	3,825	18,929	10.5 (198)	4,818	23,172	47.8 (1,107)
Chronic kidney disease						
0-19	19,007	143,995	0.3 (37)	18,200	138,410	0.2 (33)
20-39	28,896	166,662	0.8 (138)	30,555	187,402	0.9 (173)
40-49	18,626	105,218	1.9 (200)	20,119	117,418	1.4 (170)
50-59	16,546	91,726	4.2 (386)	18,264	102,861	3.1 (317)
60-69	11,049	58,474	10.1 (589)	12,300	66,388	6.8 (452)
70-79	6,896	34,352	22.4 (768)	8,330	42,336	15.0 (634)
≥ 80	3,462	16,119	52.2 (842)	5,916	31,586	31.6 (999)
Stroke						
0-19	19,044	144,494	0.1 (11)	18,225	138,714	0.1 (10)
20-39	28,966	167,513	0.2 (32)	30,625	188,279	0.3 (54)
40-49	18,723	106,112	0.9 (98)	20,195	118,033	0.9 (101)
50-59	16,663	92,757	2.3 (215)	18,316	103,296	1.9 (200)
60-69	11,095	58,984	7.1 (420)	12,326	66,626	5.3 (352)
70-79	6,787	33,726	18.1 (609)	8,155	41,474	12.9 (536)
≥ 80	3,302	16,079	26.9 (432)	5,578	29,934	24.5 (734)
Congestive heart failure						
0-19	19,049	144,577	<0.1 (3)	18,225	138,741	<0.1 (1)
20-39	28,991	167,636	0.1 (23)	30,643	188,550	0.1 (27)
40-49	18,748	106,429	0.6 (60)	20,247	118,489	0.4 (44)
50-59	16,715	93,129	2.0 (189)	18,420	104,263	1.1 (113)
60-69	11,200	60,021	4.7 (284)	12,468	67,862	3.4 (228)
70-79	7,023	35,739	14.7 (524)	8,373	43,018	10.7 (462)
≥ 80	3,454	16,474	44.4 (732)	5,644	30,042	39.2 (1,178)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 3)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Dementia						
0-19	19,045	144,233	0.7 (95)	18,224	138,612	0.5 (65)
20-39	28,927	167,098	0.5 (90)	30,613	188,229	0.4 (74)
40-49	18,730	106,234	0.8 (87)	20,234	118,263	0.7 (80)
50-59	16,732	93,398	1.2 (113)	18,391	104,060	1.2 (122)
60-69	11,339	61,016	2.4 (147)	12,527	68,389	2.2 (152)
70-79	7,250	37,024	11.5 (424)	8,523	44,015	9.0 (394)
≥ 80	3,651	17,816	37.4 (666)	5,684	30,237	43.8 (1,324)
Schizophrenia						
0-19	19,043	144,539	0.2 (32)	18,221	138,684	0.2 (28)
20-39	28,905	166,386	1.1 (177)	30,559	187,680	0.6 (116)
40-49	18,656	105,803	0.6 (68)	20,132	117,772	0.5 (53)
50-59	16,695	93,305	0.5 (49)	18,333	103,725	0.6 (67)
60-69	11,357	61,286	1.0 (59)	12,474	68,212	0.9 (61)
70-79	7,338	38,011	2.4 (92)	8,586	44,755	2.7 (121)
≥ 80	3,892	19,550	11.3 (221)	6,114	34,000	13.1 (444)
Hepatitis						
0-19	19,041	144,470	0.1 (17)	18,216	138,646	0.1 (20)
20-39	28,927	166,978	0.7 (118)	30,557	187,564	0.6 (114)
40-49	18,620	105,303	1.3 (136)	20,126	117,719	0.6 (76)
50-59	16,599	92,627	1.1 (105)	18,340	103,834	0.6 (58)
60-69	11,293	61,018	0.8 (48)	12,506	68,411	0.9 (62)
70-79	7,353	38,053	0.6 (24)	8,634	45,080	0.6 (25)
≥ 80	3,936	20,045	0.4 (9)	6,350	35,622	0.3 (12)
Autism spectrum disorder						
0-19	19,031	144,197	0.3 (37)	18,224	138,664	0.1 (16)
20-39	28,972	167,636	<0.1 (6)	30,643	188,651	<0.1 (2)
40-49	18,778	106,682	<0.1 (3)	20,275	118,760	0.0 (0)
50-59	16,810	94,079	0.0 (0)	18,480	104,783	0.0 (0)
60-69	11,424	61,702	0.0 (0)	12,603	69,065	0.0 (0)
70-79	7,409	38,416	0.0 (0)	8,704	45,493	0.0 (0)
≥ 80	3,966	20,174	0.0 (0)	6,383	35,849	0.0 (0)
Human immunodeficiency virus						
0-19	19,049	144,591	<0.1 (1)	18,227	138,772	<0.1 (1)
20-39	28,985	167,674	0.1 (20)	30,646	188,628	0.1 (11)
40-49	18,756	106,511	0.1 (13)	20,265	118,694	<0.1 (2)
50-59	16,794	94,006	<0.1 (3)	18,476	104,777	0.0 (0)
60-69	11,420	61,680	<0.1 (1)	12,603	69,065	0.0 (0)
70-79	7,408	38,407	<0.1 (1)	8,704	45,489	<0.1 (1)
≥ 80	3,964	20,171	0.0 (0)	6,383	35,849	0.0 (0)

* Incidence rates are reported per 1,000 person-years, and are calculated by dividing the number of observed new cases in parentheses by the number of observed person-years of risk within each age and sex stratum. The 20 chronic conditions are listed in decreasing order of frequency (by overall age- and sex-standardized prevalence). (Rocca et., al, 2013)

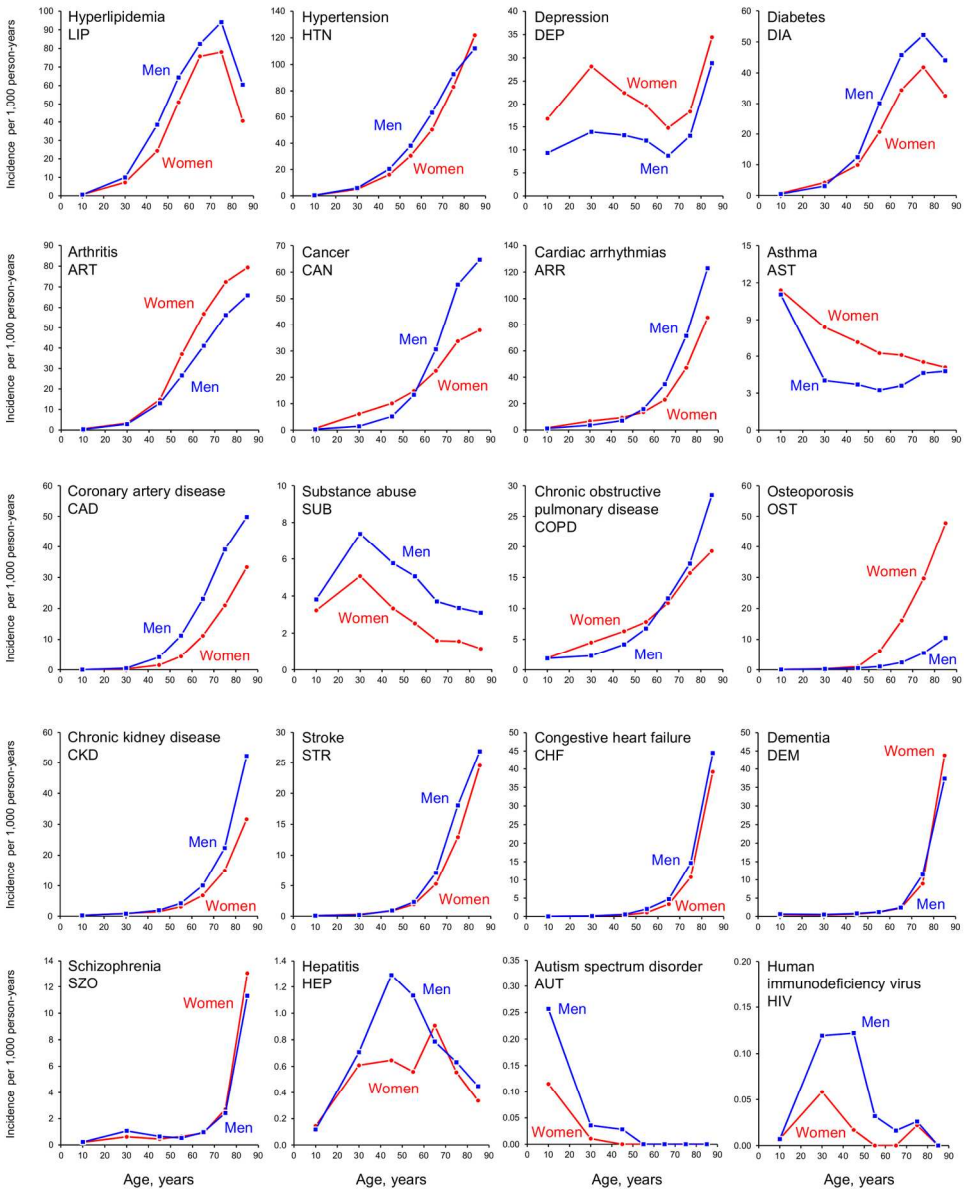


Figure 1. Age- and sex-specific incidence rates (per 1,000 person-years) of the 20 chronic conditions considered separately. The 20 panels are presented by rows in decreasing order of frequency (by overall age- and sex-standardized prevalence). 16
173x215mm (300 x 300 DPI)

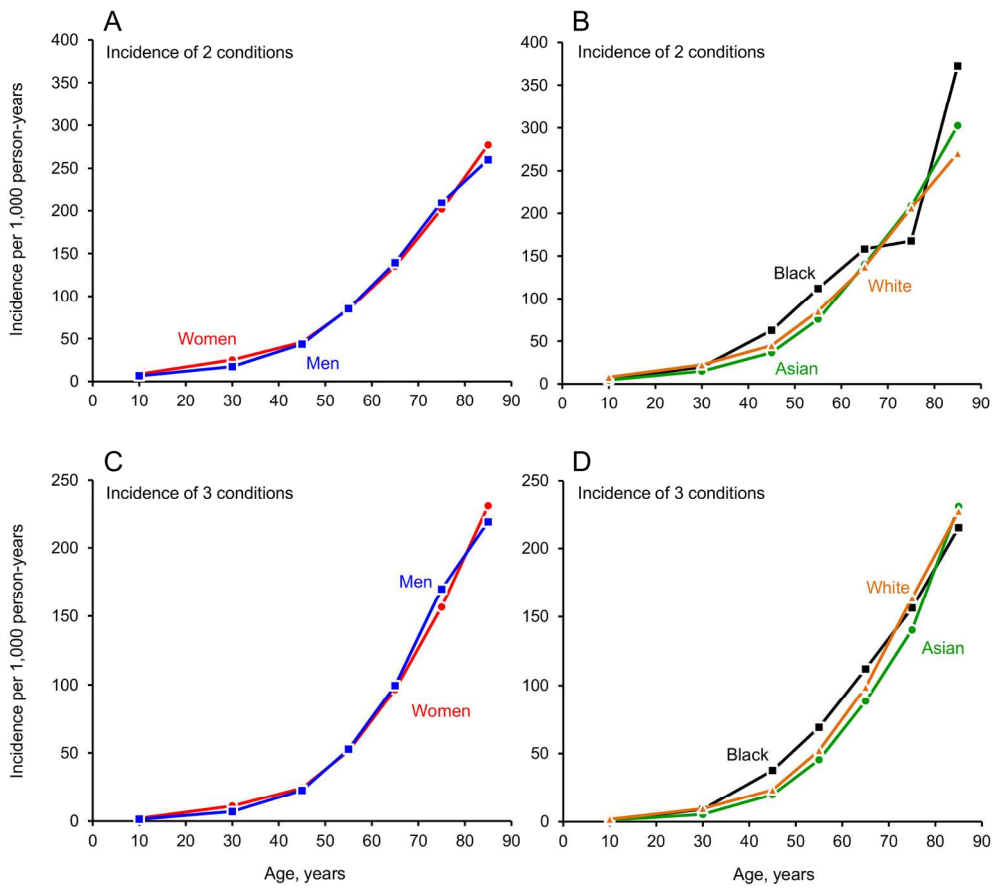


Figure 2. Incidence rates (per 1,000 person-years) of 2 chronic conditions (second condition in a dyad) and of 3 chronic conditions (third condition in a triad) in men and women separately (panels A and C), and stratified by ethnicity (panels B and D).
173x154mm (300 x 300 DPI)

Appendix 1: Supplementary tables A-C [posted as supplied by the authors]

Supplementary table A. List of the twenty chronic conditions selected by the US-DHHS *

Description †	Acronym or Abbreviation	CCC ‡	CMS (ICD-9 codes) §
Hyperlipidemia	LIP	53	272.0, 272.1, 272.2, 272.3, 272.4
Hypertension	HTN	98, 99	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 362.11, 437.2
Depression	DEP	657	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	DIA	49,50	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
Arthritis	ART	202, 203	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91
Cancer	CAN	11-43	Female breast cancer: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3. Colorectal cancer: 154.0, 154.1, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 230.3, 230.4, V10.05. Prostate cancer: 185, 233.4, V10.46. Lung cancer: 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11.
Cardiac arrhythmias	ARR	105-106	427.31
Asthma	AST	128	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Coronary artery disease	CAD	100, 101	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.8, 414.9

Supplementary table A. List of the twenty chronic conditions selected by the US-DHHS * (continued)

Description †	Acronym or Abbreviation	CCC ‡	CMS (ICD-9 codes) §
Substance abuse disorders (drug and alcohol)	SUB	660-661	Not applicable
Chronic obstructive pulmonary disease	COPD	127	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496
Osteoporosis	OST	206	733.00, 733.01, 733.02, 733.03, 733.09
Chronic kidney disease	CKD	158	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Stroke	STR	109-112	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01,434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Congestive heart failure	CHF	108	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Dementia (including Alzheimer's and other senile dementias)	DEM	653	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.8, 797
Schizophrenia	SZO	659	Not applicable
Hepatitis	HEP	6	Not applicable
Autism spectrum disorder	AUT	299.00, 299.01 ‖	Not applicable
Human immunodeficiency virus (HIV)	HIV	5	Not applicable

***** CCC = Clinical Classification Codes; CMS = Centers for Medicare and Medicaid Services; ICD-9 = International Classification of Diseases, 9th revision; US-DHHS = US Department of Health and Human Services.

† The 20 conditions were defined by the US-DHHS as detailed elsewhere. (Goodman et al., 2013) Each condition is defined by having a code in either the CCC group of codes or the CMS group of codes. Conditions are listed in decreasing order of frequency (by overall age and sex standardized prevalence; same order as in Figure 1).

‡ We list the CCC chapters developed by the Agency for Healthcare Research and Quality (AHRQ). Each CCC chapter includes a list of ICD-9 codes as detailed elsewhere. (Cohen et al., 2009)

§ We list the ICD-9 codes defined in the Chronic Conditions Data Warehouse of the CMS.

‖ Autism-spectrum disorder is not defined in either the CCC or the CMS code groupings, but rather is defined by two distinct ICD-9 codes.

Supplementary table B. Total US population used for direct standardization of incidence rates

Age	Men			Women			Adjusting population [§]
	US Total (n) *	Prev. % [†]	At risk (n) [‡]	US Total (n) *	Prev. % [†]	At risk (n) [‡]	
Prevalence of 2 chronic conditions							
0-19 y	42,592	1.26	42,054	40,675	1.40	40,108	82,162
20-39 y	41,688	6.98	38,779	41,140	8.74	37,546	76,325
40-49 y	21,603	20.37	17,202	21,995	19.71	17,660	34,862
50-59 y	20,456	38.13	12,657	21,505	35.77	13,813	26,470
60-69 y	13,930	59.41	5,654	15,323	58.35	6,381	12,036
70-79 y	7,427	79.73	1,506	9,170	78.27	1,993	3,498
≥ 80 y	4,084	87.86	496	7,152	86.41	972	1,467
Prevalence of 3 chronic conditions							
0-19 y	42,592	0.17	42,521	40,675	0.25	40,575	83,096
20-39 y	41,688	2.12	40,805	41,140	2.57	40,083	80,887
40-49 y	21,603	9.40	19,572	21,995	8.55	20,115	39,687
50-59 y	20,456	21.06	16,148	21,505	19.30	17,355	33,503
60-69 y	13,930	40.88	8,235	15,323	38.32	9,452	17,687
70-79 y	7,427	65.11	2,591	9,170	62.05	3,480	6,071
≥ 80 y	4,084	78.93	861	7,152	74.17	1,848	2,708

* Population (in thousands) of the entire United States from the decennial census of 2010.
† Prevalence of 2 or 3 chronic conditions from our previous study in Olmsted County, MN. (Rocca et., al, In Press)
‡ Total population at risk (in thousands) after removing the estimated prevalent persons who have already reached 2 or 3 chronic conditions.
§ The total population (in thousands) used in Tables 1 and 2 for direct standardization.

Supplementary table C. Incidence of twenty chronic conditions considered individually

Condition age (years)	Men Persons	Men Person-years	Men Incidence rate * (n)	Women Persons	Women Person-years	Women Incidence rate * (n)
Hyperlipidemia						
0-19	18,996	143,882	0.6 (91)	18,174	138,140	0.7 (94)
20-39	28,437	159,373	10.0 (1,586)	30,040	179,745	7.3 (1,311)
40-49	16,512	82,705	38.5 (3,186)	18,328	99,834	24.3 (2,428)
50-59	11,993	54,436	64.4 (3,504)	14,248	68,637	51.0 (3,500)
60-69	6,023	25,216	82.4 (2,077)	7,111	30,967	75.7 (2,345)
70-79	3,077	11,661	94.1 (1,097)	3,821	14,970	78.0 (1,168)
≥ 80	1,712	7,163	60.5 (433)	3,319	15,777	40.6 (641)
Hypertension						
0-19	19,029	144,237	0.5 (65)	18,215	138,569	0.4 (51)
20-39	28,626	162,582	5.9 (954)	30,315	183,220	5.0 (908)
40-49	17,289	92,372	20.4 (1,882)	18,790	105,079	16.0 (1,683)
50-59	13,481	67,250	38.0 (2,556)	15,013	77,172	30.3 (2,341)
60-69	7,077	31,540	63.2 (1,993)	7,971	36,990	50.3 (1,859)
70-79	3,331	13,402	92.6 (1,241)	3,941	16,136	83.0 (1,339)
≥ 80	1,354	5,198	112.0 (582)	2,053	7,919	121.9 (965)
Depression						
0-19	18,794	139,315	9.3 (1,297)	17,774	131,126	16.8 (2,198)
20-39	27,342	150,493	13.9 (2,091)	27,026	146,257	28.2 (4,118)
40-49	17,234	94,033	13.2 (1,238)	16,533	89,742	22.4 (2,013)
50-59	15,027	81,059	12.0 (974)	14,642	77,962	19.6 (1,530)
60-69	10,174	54,355	8.7 (472)	10,229	54,471	14.8 (805)
70-79	6,720	34,274	13.0 (447)	7,408	37,536	18.3 (688)
≥ 80	3,482	17,009	28.9 (491)	5,313	28,290	34.4 (974)
Diabetes						
0-19	19,025	144,155	0.5 (68)	18,190	138,186	0.7 (90)
20-39	28,799	165,115	3.0 (503)	30,406	184,616	4.2 (775)
40-49	18,193	100,104	12.4 (1,246)	19,617	112,231	9.9 (1,112)
50-59	15,419	80,259	30.1 (2,417)	17,181	92,695	20.7 (1,917)
60-69	9,394	45,589	45.7 (2,084)	10,854	55,408	34.4 (1,906)
70-79	5,427	25,396	52.2 (1,326)	6,966	33,383	41.8 (1,395)
≥ 80	2,840	13,550	44.1 (597)	5,074	26,909	32.6 (876)
Arthritis						
0-19	19,032	144,320	0.3 (49)	18,205	138,450	0.5 (68)
20-39	28,827	165,354	2.9 (477)	30,425	185,391	3.4 (625)
40-49	18,202	99,821	13.0 (1,298)	19,464	109,658	14.8 (1,628)
50-59	15,324	79,753	26.6 (2,120)	16,304	83,158	37.0 (3,079)
60-69	9,295	45,576	41.1 (1,874)	9,227	43,244	56.8 (2,458)
70-79	5,193	23,106	56.3 (1,300)	5,185	22,090	72.3 (1,598)
≥ 80	2,317	9,836	65.9 (648)	3,252	14,434	79.4 (1,146)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 1)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Cancer						
0-19	19,020	144,181	0.3 (40)	18,180	138,347	0.6 (84)
20-39	28,832	166,077	1.5 (241)	29,734	176,247	6.1 (1,079)
40-49	18,402	103,035	5.2 (534)	18,658	105,898	10.1 (1,072)
50-59	15,899	85,763	13.4 (1,145)	16,361	89,149	14.8 (1,321)
60-69	9,821	49,157	30.7 (1,507)	10,480	54,117	22.5 (1,215)
70-79	5,146	23,169	55.3 (1,281)	6,552	31,563	33.7 (1,065)
≥ 80	2,112	9,137	64.7 (591)	4,411	21,933	38.0 (833)
Cardiac arrhythmias						
0-19	19,008	143,802	1.2 (170)	18,203	137,966	1.7 (228)
20-39	28,736	164,530	3.6 (590)	30,250	181,665	6.7 (1,216)
40-49	18,324	102,268	7.1 (722)	19,444	110,842	9.3 (1,036)
50-59	15,939	85,675	15.8 (1,354)	17,211	94,404	13.5 (1,274)
60-69	10,068	50,190	34.7 (1,741)	11,262	58,346	22.9 (1,337)
70-79	5,514	24,370	71.4 (1,741)	7,095	33,211	47.1 (1,563)
≥ 80	2,193	8,604	122.9 (1,057)	4,365	20,213	85.6 (1,731)
Asthma						
0-19	17,856	126,216	11.1 (1,395)	17,443	125,314	11.4 (1,428)
20-39	27,126	155,022	4.0 (624)	28,383	168,182	8.4 (1,409)
40-49	18,102	101,654	3.7 (376)	18,845	107,595	7.2 (770)
50-59	16,129	89,329	3.2 (289)	16,920	94,186	6.3 (589)
60-69	10,930	58,658	3.6 (211)	11,535	62,226	6.1 (379)
70-79	7,051	36,059	4.6 (167)	7,987	41,216	5.5 (228)
≥ 80	3,741	18,815	4.8 (90)	5,878	32,584	5.1 (166)
Coronary artery disease						
0-19	19,050	144,593	0.0 (0)	18,227	138,785	0.0 (0)
20-39	28,982	167,484	0.5 (79)	30,647	188,499	0.3 (50)
40-49	18,565	104,424	4.1 (432)	20,213	117,920	1.5 (177)
50-59	15,875	85,866	11.2 (963)	18,177	101,860	4.4 (446)
60-69	9,540	47,996	23.1 (1,108)	11,891	62,970	11.2 (703)
70-79	5,081	23,713	39.1 (927)	7,473	37,099	21.0 (779)
≥ 80	2,213	10,046	49.8 (500)	4,868	25,325	33.4 (845)
Substance abuse disorders						
0-19	18,850	142,916	3.8 (545)	18,083	137,309	3.2 (443)
20-39	28,004	157,109	7.4 (1,159)	29,846	179,474	5.1 (910)
40-49	18,038	100,943	5.8 (582)	19,722	114,415	3.3 (381)
50-59	16,085	89,151	5.1 (451)	18,013	101,745	2.5 (257)
60-69	11,001	59,373	3.7 (220)	12,398	67,817	1.6 (108)
70-79	7,194	37,259	3.4 (125)	8,599	44,899	1.6 (70)
≥ 80	3,882	19,697	3.1 (61)	6,325	35,542	1.2 (41)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 2)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Chronic obstructive pulmonary disease						
0-19	18,973	142,682	1.9 (267)	18,140	136,992	1.9 (263)
20-39	28,674	164,415	2.3 (376)	30,052	181,106	4.5 (811)
40-49	18,348	103,031	4.2 (430)	19,432	111,533	6.3 (704)
50-59	16,170	88,965	6.7 (600)	17,425	96,719	7.8 (756)
60-69	10,615	55,796	11.6 (648)	11,556	61,640	10.9 (670)
70-79	6,439	32,418	17.2 (559)	7,661	38,688	15.7 (608)
≥ 80	3,234	15,771	28.5 (449)	5,397	29,472	19.3 (568)
Osteoporosis						
0-19	19,048	144,579	<0.1 (5)	18,226	138,759	<0.1 (5)
20-39	28,982	167,571	0.2 (41)	30,631	188,380	0.3 (58)
40-49	18,740	106,337	0.5 (53)	20,191	117,986	1.0 (119)
50-59	16,745	93,377	1.1 (99)	18,194	101,448	6.2 (628)
60-69	11,326	60,849	2.4 (144)	11,750	61,299	16.1 (987)
70-79	7,280	37,236	5.5 (206)	7,330	34,844	29.7 (1,034)
≥ 80	3,825	18,929	10.5 (198)	4,818	23,172	47.8 (1,107)
Chronic kidney disease						
0-19	19,007	143,995	0.3 (37)	18,200	138,410	0.2 (33)
20-39	28,896	166,662	0.8 (138)	30,555	187,402	0.9 (173)
40-49	18,626	105,218	1.9 (200)	20,119	117,418	1.4 (170)
50-59	16,546	91,726	4.2 (386)	18,264	102,861	3.1 (317)
60-69	11,049	58,474	10.1 (589)	12,300	66,388	6.8 (452)
70-79	6,896	34,352	22.4 (768)	8,330	42,336	15.0 (634)
≥ 80	3,462	16,119	52.2 (842)	5,916	31,586	31.6 (999)
Stroke						
0-19	19,044	144,494	0.1 (11)	18,225	138,714	0.1 (10)
20-39	28,966	167,513	0.2 (32)	30,625	188,279	0.3 (54)
40-49	18,723	106,112	0.9 (98)	20,195	118,033	0.9 (101)
50-59	16,663	92,757	2.3 (215)	18,316	103,296	1.9 (200)
60-69	11,095	58,984	7.1 (420)	12,326	66,626	5.3 (352)
70-79	6,787	33,726	18.1 (609)	8,155	41,474	12.9 (536)
≥ 80	3,302	16,079	26.9 (432)	5,578	29,934	24.5 (734)
Congestive heart failure						
0-19	19,049	144,577	<0.1 (3)	18,225	138,741	<0.1 (1)
20-39	28,991	167,636	0.1 (23)	30,643	188,550	0.1 (27)
40-49	18,748	106,429	0.6 (60)	20,247	118,489	0.4 (44)
50-59	16,715	93,129	2.0 (189)	18,420	104,263	1.1 (113)
60-69	11,200	60,021	4.7 (284)	12,468	67,862	3.4 (228)
70-79	7,023	35,739	14.7 (524)	8,373	43,018	10.7 (462)
≥ 80	3,454	16,474	44.4 (732)	5,644	30,042	39.2 (1,178)

Supplementary table C. Incidence of twenty chronic conditions considered individually (continued 3)

Condition age (years)	Men			Women		
	Persons	Person-years	Incidence rate * (n)	Persons	Person-years	Incidence rate * (n)
Dementia						
0-19	19,045	144,233	0.7 (95)	18,224	138,612	0.5 (65)
20-39	28,927	167,098	0.5 (90)	30,613	188,229	0.4 (74)
40-49	18,730	106,234	0.8 (87)	20,234	118,263	0.7 (80)
50-59	16,732	93,398	1.2 (113)	18,391	104,060	1.2 (122)
60-69	11,339	61,016	2.4 (147)	12,527	68,389	2.2 (152)
70-79	7,250	37,024	11.5 (424)	8,523	44,015	9.0 (394)
≥ 80	3,651	17,816	37.4 (666)	5,684	30,237	43.8 (1,324)
Schizophrenia						
0-19	19,043	144,539	0.2 (32)	18,221	138,684	0.2 (28)
20-39	28,905	166,386	1.1 (177)	30,559	187,680	0.6 (116)
40-49	18,656	105,803	0.6 (68)	20,132	117,772	0.5 (53)
50-59	16,695	93,305	0.5 (49)	18,333	103,725	0.6 (67)
60-69	11,357	61,286	1.0 (59)	12,474	68,212	0.9 (61)
70-79	7,338	38,011	2.4 (92)	8,586	44,755	2.7 (121)
≥ 80	3,892	19,550	11.3 (221)	6,114	34,000	13.1 (444)
Hepatitis						
0-19	19,041	144,470	0.1 (17)	18,216	138,646	0.1 (20)
20-39	28,927	166,978	0.7 (118)	30,557	187,564	0.6 (114)
40-49	18,620	105,303	1.3 (136)	20,126	117,719	0.6 (76)
50-59	16,599	92,627	1.1 (105)	18,340	103,834	0.6 (58)
60-69	11,293	61,018	0.8 (48)	12,506	68,411	0.9 (62)
70-79	7,353	38,053	0.6 (24)	8,634	45,080	0.6 (25)
≥ 80	3,936	20,045	0.4 (9)	6,350	35,622	0.3 (12)
Autism spectrum disorder						
0-19	19,031	144,197	0.3 (37)	18,224	138,664	0.1 (16)
20-39	28,972	167,636	<0.1 (6)	30,643	188,651	<0.1 (2)
40-49	18,778	106,682	<0.1 (3)	20,275	118,760	0.0 (0)
50-59	16,810	94,079	0.0 (0)	18,480	104,783	0.0 (0)
60-69	11,424	61,702	0.0 (0)	12,603	69,065	0.0 (0)
70-79	7,409	38,416	0.0 (0)	8,704	45,493	0.0 (0)
≥ 80	3,966	20,174	0.0 (0)	6,383	35,849	0.0 (0)
Human immunodeficiency virus						
0-19	19,049	144,591	<0.1 (1)	18,227	138,772	<0.1 (1)
20-39	28,985	167,674	0.1 (20)	30,646	188,628	0.1 (11)
40-49	18,756	106,511	0.1 (13)	20,265	118,694	<0.1 (2)
50-59	16,794	94,006	<0.1 (3)	18,476	104,777	0.0 (0)
60-69	11,420	61,680	<0.1 (1)	12,603	69,065	0.0 (0)
70-79	7,408	38,407	<0.1 (1)	8,704	45,489	<0.1 (1)
≥ 80	3,964	20,171	0.0 (0)	6,383	35,849	0.0 (0)

* Incidence rates are reported per 1,000 person-years, and are calculated by dividing the number of observed new cases in parentheses by the number of observed person-years of risk within each age and sex stratum. The 20 chronic conditions are listed in decreasing order of frequency (by overall age- and sex-standardized prevalence). (Rocca et., al, 2013)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	14-17
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9, 16
		(*e*) Describe any sensitivity analyses	10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13, Tables 1-3, Figures 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Tables 1-3, Figures 1 and 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.