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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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Manuscripts

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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21 **Corresponding Author:** Walter A. Rocca, MD, MPH, Division of Epidemiology,
22 Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester,
23 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

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3 overall risk was similar in men and women; however, the combinations of conditions
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5 (dyads and triads) differed extensively by age and by sex. Compared to Whites, the
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7 incidence of multimorbidity was higher in Blacks and lower in Asians.
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12 **Conclusions:** The risk of developing de novo multimorbidity increases steeply with
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14 older age, varies by ethnicity, and is similar in men and women overall. However, the
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16 combinations of conditions vary extensively by age and sex. These data represent an
17
18 important first step toward identifying the causes and the consequences of
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20 multimorbidity.
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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

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3 public health priority for the nation.¹⁵ The Rochester Epidemiology Project (REP)
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5 medical records-linkage system captures long-term medical information on a stable
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7 population, and is therefore uniquely positioned to study the incidence of multimorbidity.
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9 In a previous paper, we described in detail the patterns of prevalent multimorbidity in
10
11 this population.¹⁶ In this study, we further leveraged this data resource to examine the
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13 incidence of multimorbidity across all ages, separately in men and women, and in three
14
15 ethnic groups.¹⁷
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22 **METHODS**

23 **Study population**

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28 The REP has tracked and linked health care information for the population of Olmsted
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30 County, MN, since 1966.¹⁷⁻¹⁹ The vast majority of medical care in this community is
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32 currently provided by a few health care institutions: Olmsted Medical Center and its
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34 affiliated hospital, Mayo Clinic and its two affiliated hospitals, the Rochester Family
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36 Medicine Clinic, and a few smaller care facilities. The health care records from these
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38 institutions are linked together through the REP records-linkage system.¹⁷⁻¹⁹ Persons
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40 are considered residents of Olmsted County at the time of each health care visit based
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42 on their address. Over the years, this address information has been accumulated and
43
44 is used to define who resided in Olmsted County at any given point in time since 1966
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46 (REP Census). The population counts obtained by the REP Census are similar to those
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48 obtained by the US Census, indicating that virtually the entire population of the county is
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50 captured by the system.¹⁸⁻²⁰ We used the REP Census to identify all individuals who
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52 resided in Olmsted County on January 1, 2000 (baseline date); however, we included
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3 only individuals who had not refused permission to use their medical records for
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5 research (Minnesota research authorization).^{18,21,22}
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10 **Definition of incident multimorbidity**

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12 We focused on 20 selected chronic conditions recommended by the US-DHHS for
13
14 studying multimorbidity.^{23,24} The list of the 20 conditions and the corresponding ICD-9
15
16 codes used in this study are provided in Supplementary Table A.^{23,24,23,24} We first
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18 identified all ICD-9 codes associated with these 20 chronic conditions that occurred in
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20 the population between January 1, 1995 and December 31, 1999 (5 years before the
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22 baseline date, January 1, 2000). Persons who did not have any ICD-9 code for a given
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24 condition were assumed to not have the condition of interest. By contrast, residents
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26 were defined as having a chronic condition if they had at least two ICD-9 codes for that
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28 condition separated by more than 30 days, and the incidence date was assigned at the
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30 time they received a second diagnostic code.
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38 Persons who had 2 or more of the 20 conditions at baseline were considered to
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40 have prevalent multimorbidity and were therefore excluded from incidence analyses of 2
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42 chronic conditions (dyads). Similarly, persons who had 3 or more of the 20 conditions
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44 at baseline were excluded from incidence analyses of 3 chronic conditions (triads). All
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46 persons in this fixed population cohort were followed historically through the REP
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48 records-linkage system for approximately 14 years to study the emergence of new
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50 conditions.
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56 **Statistical Analyses**

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3 All persons in the cohort were followed from January 1, 2000 through the last contact
4 with the records-linkage system (the earliest of death date, last medical visit date, or
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6 December 31, 2013). The incidence of each of the 20 chronic conditions was
7
8 calculated among persons free of that condition at baseline. Persons contributed
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10 person-years to the denominator for the incidence of 2 conditions (development of a
11
12 second condition in a dyad) only during the time when they had 0 or 1 chronic
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14 conditions, whereas persons contributed person-years to the denominator for the
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16 incidence of 3 chronic conditions (development of a third condition in a triad) only when
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18 they had 0, 1, or 2 chronic conditions. Although the majority of people accumulated
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20 conditions one-at-a-time, some subjects jumped from 0 to 2 conditions, or from 1 to 3,
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22 or even from 0 to 3 conditions. For example, a person previously considered free of all
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24 of the 20 conditions who was diagnosed with hyperlipidemia, hypertension, and
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26 depression during one visit was counted both as an incident dyad and as an incident
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28 triad on the same date.
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36 Incidence rates were reported separately by age (using seven age strata or
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38 splitting the entire population in 0-64 and ≥ 65 years), sex, and ethnicity, and were
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40 directly standardized by age and sex to the total US 2010 Decennial Census after
41
42 removing projected prevalence (see Supplementary Table B). Because the study
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44 covered the target population completely, and no sampling was involved, confidence
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46 intervals were not included in the tables.^{25 26} Ethnicity data were not available for 9,176
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48 people (7.4% of the cohort). These individuals were included in the overall and age-
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50 and sex-specific analyses, but not in the ethnicity-specific analyses.
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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

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

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25 Figure 2 shows the age-specific incidence rates of multimorbidity in men and women
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27 separately (panels A and C), and in three ethnic groups (panels B and D). Both the
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29 incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased
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31 steeply with older age (Table 1, Table 2, and Figure 2). For example, the incidence of 2
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33 chronic conditions in men was 6.5/1,000 person-years in persons who were ages 0-19
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35 years, and 260.0/1,000 in persons who were ≥ 80 years. The overall incidence of 2
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37 chronic conditions was slightly higher in women compared to men (overall standardized
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39 incidence rates 38.8 vs. 35.5/1,000 person-years; Table 1). The incidence of 2 chronic
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41 conditions was higher in Blacks compared to Whites, but lower in Asians compared to
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43 Whites (standardized incidence rates; Table 1 and Figure 2). We observed similar
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45 patterns for the development of 3 chronic conditions (Table 2 and Figure 2). The overall
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47 incidence of 3 conditions was similar in men and women (standardized incidence rates
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49 25.5/1,000 person-years in men vs. 26.6/1,000 person-years in women); however, it
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51 was higher in Blacks and lower in Asians, compared to Whites (Figure 2).
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3 In the set of sensitivity analyses in which we combined hyperlipidemia and
4 hypertension as a single condition, we observed a slight decrease in the incidence of 2
5 chronic conditions and of 3 chronic conditions compared with the primary analyses.
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7 The overall incidence rate of 2 conditions decreased from 35.0 to 34.0/1,000 person-
8 years in men and from 40.3 to 40.0/1,000 person-years in women. The incidence rate
9 of 3 conditions decreased from 24.7 to 22.5/1,000 person-years in men and from 28.5 to
10 27.0/1,000 person-years in women (incidence rates non-standardized; data not shown
11 in the Tables). For both 2 and 3 conditions, the decrease in incidence was more
12 sizeable in men than in women.
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24 25 26 27 **Incidence of dyads and triads**

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30 Table 3 shows the incidence of the most common dyads or triads of chronic conditions
31 in seven age strata and for men and women separately. The incidence of dyads and
32 triads varied extensively with age. For example, the most common incident dyad in
33 persons 0-19 years was depression and asthma (1.8/1,000 person-years in boys or
34 men and 2.9/1,000 person-years in girls or women). By comparison, the most common
35 dyad in persons ≥ 80 years was hypertension and cancer in men (18.9/1,000 person-
36 years) and hypertension and arthritis in women (27.7/1,000 person-years). Similarly,
37 the most common incident triad of conditions in persons aged 0-19 years was
38 depression, asthma, and substance abuse disorders in both sexes. By comparison, the
39 most common incident triads in persons ≥ 80 years were hypertension, cancer, and
40 arrhythmia in men and hyperlipidemia, hypertension, and arthritis in women.
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3 The incidence of dyads and triads also varied by sex. In some instances, the
4 composition of the dyads or triads was the same for men and women, but the
5 magnitude of the incidence rate was different. In other instances, the magnitude of the
6 incidence rate was similar in men and women, but the composition of the dyads and
7 triads varied by sex. For example, the most common incident dyad in persons aged 60-
8 69 years was hyperlipidemia and hypertension in both sexes, but the incidence rate was
9 higher in men compared to women (23.4/1,000 person-years vs. 18.8/1,000 person-
10 years). By contrast, the incidence rates of the most common triads in persons aged 60-
11 69 years were similar in men and women (11.6/1,000 vs. 10.3/1,000 person-years);
12 however, they included different conditions (Table 3).
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29 **DISCUSSION**

30 **Statement of the principal findings**

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32 The burden of multimorbidity in the United States is high and is increasing with an aging
33 population and with improvements in survival. We leveraged a unique longitudinal data
34 resource covering an entire stable and geographically defined population to examine
35 the incidence of multimorbidity across all ages. The incidence of 2 chronic conditions
36 and the incidence of 3 chronic conditions increased steeply with older age, and the
37 overall risk was similar in men and women. However, the number of people who
38 developed multimorbidity before age 65 was more than four times greater than the
39 number of people who developed multimorbidity after age 65. The incidence of
40 multimorbidity was highest in Blacks, and lowest in Asians. Finally, the combinations of
41 conditions in incident dyads and triads differed extensively by age and by sex. These
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3 results have important implications for identifying individuals at higher risk of developing
4 multimorbidity at different ages. These data are also a first step toward understanding
5 the causes and the consequences of multimorbidity.
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10 11 12 **Strengths and weaknesses**

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16 A unique strength of our study was the ability to measure the incidence of multimorbidity
17 documented in medical records across seven age groups and for an entire,
18 geographically defined population. We used historical data both to exclude individuals
19 with prevalent multimorbidity at baseline and to follow individuals over a long period of
20 time to accurately document the development of incident multimorbidity. In total, our
21 findings reflect 19 years of data accumulation (5 years before and 14 years after the
22 baseline date).
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33 Unfortunately, there is no standard definition of multimorbidity. Previous studies
34 have included a wide range of chronic conditions and a wide range of time frames. We
35 defined multimorbidity using the 20 conditions selected by US-DHHS which were
36 chosen because they “meet the definition for chronicity, are prevalent [common], and
37 are potentially amenable to public health or clinical interventions or both.”²³ However,
38 this definition provides equal weight to each of the 20 conditions without considering the
39 impact of combinations of specific conditions on the quality of life of patients, the
40 complexity of their joint management, and the severity of their long-term outcomes.
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52 Some of the dyads and triads derived by the combination of the 20 conditions
53 selected by the US-DHHS may have a much stronger impact on the complexity of
54 clinical management than others.²⁷ Therefore, some dyads or triads may be
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3 particularly costly for the health system, harder for the patient to manage by
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5 themselves, less amenable to a single disease approach to care (e.g., telemonitoring for
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7 heart failure), and may have a stronger effect on functionality, severity of symptoms,
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9 and risk of death. In addition, social (e.g., inadequate insurance, low education) and
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11 behavioral factors (e.g., poor diet) not reflected in the list of 20 US-DHHS conditions
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13 may be as important, or more important, than the 20 conditions in determining the
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15 complexity of clinical management and long-term outcomes.²⁷
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20 For example, because hyperlipidemia and hypertension are typically
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22 asymptomatic, and are often diagnosed as the result of routine screening, their
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24 combination is likely to have a much lower impact on the life of the patient than the
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26 combination of schizophrenia and heart failure. However, both combinations are
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28 considered multimorbidity by the US-DHHS definition. Our sensitivity analyses highlight
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30 this problem. As expected, when hyperlipidemia and hypertension were considered as
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32 a single condition, the overall incidence of multimorbidity decreased. The decreases
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34 were relatively small but were more sizeable in men than in women. These findings
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36 emphasize the importance of reaching consensus on the list of conditions to be used to
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38 define multimorbidity. However, it is difficult to assess the utility of the 20 conditions
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40 included in the US-DHHS list without also understanding how different combinations of
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42 these conditions impact long term outcomes. Therefore, we plan to continue this initial
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44 incidence study with further analyses to assess which combinations of conditions have
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46 the greatest impact on adverse outcomes, including patient quality of life and complexity
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48 of clinical management.²⁷
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3 We defined incident multimorbidity as the date on which a person met the criteria
4 for a second condition or for a third condition. We used an approach similar to that
5 used in the definition for the onset of metabolic syndrome (reaching three of five
6 components of the syndrome).^{28,29} This simple operational definition of incident
7 multimorbidity should be easy to replicate, and should facilitate future comparisons with
8 other populations.
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11 Potential weaknesses of our study include the inability to validate the ICD-9
12 codes. It was not possible to confirm all diagnoses for the entire study population, and
13 some ICD-9 codes may have been assigned in error (e.g., “rule out” diagnostic codes).
14 To reduce the likelihood of a single ICD-9 code error, we required two or more
15 diagnosis codes separated by more than 30 days for a person to be defined as having a
16 condition.³⁰ However, if a person received a valid code and was lost to follow-up or
17 died rapidly after diagnosis, we may have underestimated the incidence of some of the
18 conditions. In addition, we used diagnosis date as a proxy for the true date of onset of
19 the condition.
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23 Some individuals may have moved into Olmsted County after having been
24 diagnosed with one or more chronic conditions elsewhere. If those persons continued
25 to receive care within the REP for a number of years, we captured their chronic
26 condition at the time of subsequent health care visits. However, we did not know the
27 true date of onset for the condition, and the sequence of accumulation of conditions
28 could be distorted. Because the population of Olmsted County is stable, particularly
29 among persons who are 40 years of age or older,¹⁹ we do not expect a major distortion
30 of multimorbidity incidence rates due to migration.
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4 Finally, our study focused on a single geographically defined US population, and
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6 the incidence of multimorbidity may differ in other populations. However, the
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8 demographic and socioeconomic characteristics of our population are similar to those of
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10 the upper Midwest of the United States,²⁰ and the prevalence of multimorbidity in
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12 persons 65 years of age or older was similar in our population compared with the entire
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14 US Medicare population.¹⁶ Replication of this study in other populations in the United
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16 States and worldwide will allow for useful comparisons.
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22 **Comparison with other studies**

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25 A number of studies have described the prevalence of multimorbidity in various
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27 populations;^{1,7-12} however, few studies have described the incidence of multimorbidity,
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29 and no incidence studies are available for the US. In 1998, Van den Akker and
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31 colleagues estimated the one year incidence of multimorbidity in patients from a
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33 network of family practices in the Netherlands.³¹ Incident multimorbidity was defined as
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35 the new development of at least 2 of 335 diagnostic categories within a one year period.
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37 Overall, 7.9% of their population developed one new disease and 1.3% developed two
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39 or more new diseases in one year. The proportion of people who developed two or
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41 more new conditions increased with older age, but did not differ substantially by sex. It
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43 is difficult to compare our results directly to the Dutch findings because of
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45 methodological differences (e.g., number of conditions considered and time frame), and
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47 because it is not clear whether some of the participants in the Dutch study already had
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49 one or more conditions at baseline. However, we observed similar patterns of
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3 increasing incidence with older age, and limited differences between men and women in
4 overall incidence.
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8 More recently, Melis and colleagues assessed the incidence of multimorbidity in
9 Swedish people aged 75 years or older at baseline who participated in a longitudinal
10 cohort study.³² Incident multimorbidity was defined as the development of at least 2 of
11 39 chronic conditions during three years of follow-up. Participants with none of the 39
12 chronic conditions at baseline had a multimorbidity incidence rate of 12.6 per 100
13 person-years, and patients with one of the 39 conditions at baseline had an incidence
14 rate of 32.9 per 100 person-years. Although we examined fewer conditions than the
15 Swedish group (20 vs. 39), and the ascertainment of incident conditions was different
16 (medical records data vs. survey methods), our incidence rates of multimorbidity in
17 subjects aged 75 years or older were similar (19.1 per 100 person-years in people with
18 no conditions at baseline and 38.9 per 100 person-years in persons with one condition
19 at baseline; both sexes combined; data not shown).
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41 **Meaning of the study**

42 To understand the importance of these findings, we draw an analogy with the difference
43 between prevalence and incidence in epidemiologic studies considering one disease at
44 a time.^{33,34} Incidence is the direct measure of the risk of people to develop a given
45 disease, whereas prevalence is the percent of people affected by the same disease at
46 one point in time, and reflects both the effect of incidence and the effect of survival after
47 the onset of the disease.^{33,34} Similarly, the prevalence of multimorbidity gives us a
48 static picture of the population; however, prevalence may be misleading when studying
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3 the mechanisms of multimorbidity. For example, a higher prevalence of multimorbidity
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5 in women than in men may be due to a higher risk of women developing multimorbidity,
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7 or to a longer survival of women affected by multimorbidity.¹⁶ By contrast, a higher
8
9 incidence of multimorbidity in women compared to men points directly to a difference in
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11 risk (assuming that access to care is comparable in the sexes).
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15 Prior studies of the prevalence of multimorbidity have shown a dramatic increase
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17 in the number of people living with 2 or more chronic conditions at older ages.^{1,7-11}
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19 However, the high prevalence of multimorbidity in the older population implies that
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21 relatively few older individuals remain at risk of developing multimorbidity. Overall,
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23 among persons aged ≥ 80 years at baseline, only 891 out of 3,710 (24.0%) were at risk
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25 of developing 2 chronic conditions (the other 76.0% already had 2 or more of the 20
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27 conditions). Therefore, the persons who reached 80 years of age or older and
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29 remained free of multimorbidity represent an ideal population in which to study
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31 successful aging and resiliency.
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35 We also found that the total number of people who developed multimorbidity
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37 before age 65 years was more than 4 times greater than the number of people who
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39 developed multimorbidity at age 65 or older (28,378 vs. 6,214). These data emphasize
40
41 the need to target preventive efforts at much younger ages, but represent only a first
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43 step toward future research to identify the social, behavioral, and clinical risk and
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45 protective factors for multimorbidity.
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50 We found important differences in the incidence of multimorbidity by ethnicity.
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52 The age standardized incidence rates of multimorbidity were higher in Blacks and lower
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54 in Asians compared to Whites. Our findings are consistent with previous studies that
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3 showed a higher prevalence of multimorbidity in Blacks compared to Whites, but a lower
4 prevalence of multimorbidity in Asians.^{8,16,35-37} Our data suggest that some of these
5 differences in prevalence may be attributed to differences in the incidence of the
6 conditions among different ethnic groups. However, differential survival may also
7 contribute to the differences in prevalence, which, in turn, may be influenced by
8 socioeconomic factors, lifestyle behaviors, social environment, and healthcare access.
9 Further research is needed to better characterize these disparities and to identify the
10 causal mechanisms that contribute to different development of chronic conditions and to
11 different survival.
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24 The incidence and the composition of the dyads and triads of conditions varied
25 extensively across age and sex strata. For example, women 20 years of age or older
26 were more likely to have depression as a component of their incident multimorbidity
27 dyads and triads compared to men. Such differences may lead to different long-term
28 outcomes in men and women. Therefore, these data are useful to understand how
29 multimorbidity develops, and are an important first step toward future research. In
30 particular, such incident data are necessary to study the chronological order of
31 acquisition of multiple chronic conditions in different age, sex, and ethnic strata.
32 Incidence data are also necessary to determine whether the differential order of
33 acquisition is associated with a different risk of adverse long-term outcomes such as
34 hospitalizations, emergency department visits, or death. For example, it is not clear
35 whether acquiring depression prior to arthritis results in worse long-term outcomes
36 compared with acquiring arthritis prior to depression. Future studies are also needed to
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3 understand how additional chronic conditions accumulate after the development of a
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5 second and third condition.
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10 **Conclusions and clinical implications**

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

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

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

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3 *Study supervision:* Yawn, Rocca.
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6 **Identifiable patients:** No identifiable patients were included.
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3 **Responsibility for the integrity of the data:** All authors, external and internal, had full
4
5 access to all of the data (including statistical reports and tables) in the study and can
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7 take responsibility for the integrity of the data and the accuracy of the data analysis.
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11 **Transparency declaration:** The lead author (the manuscript's guarantor, Dr. JLS)
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13 affirms that the manuscript is an honest, accurate, and transparent account of the study
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15 being reported; that no important aspects of the study have been omitted; and that any
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21 **Data sharing:** No additional data available.
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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.

Ethnicity age (years)	Men			Women		
	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

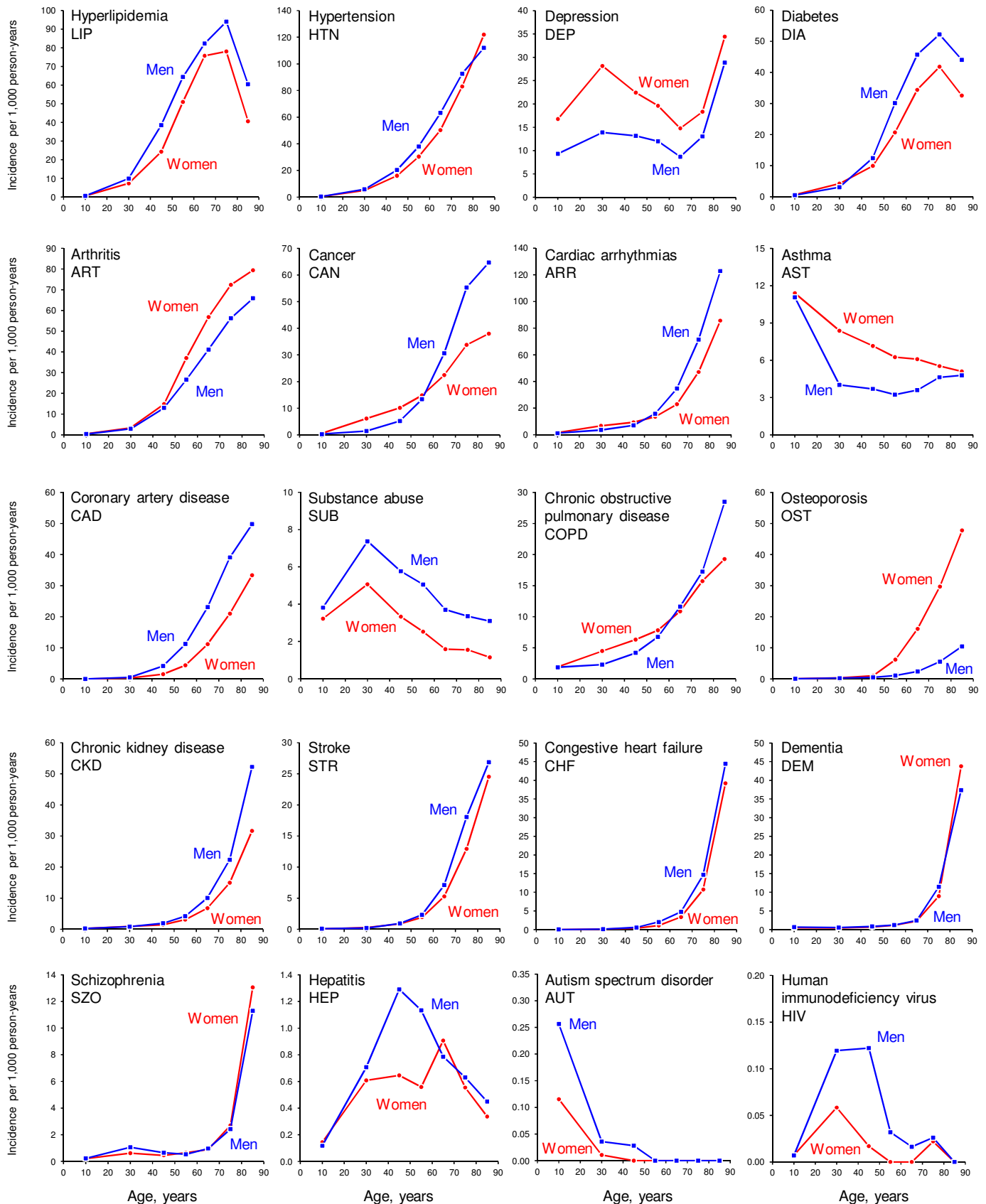
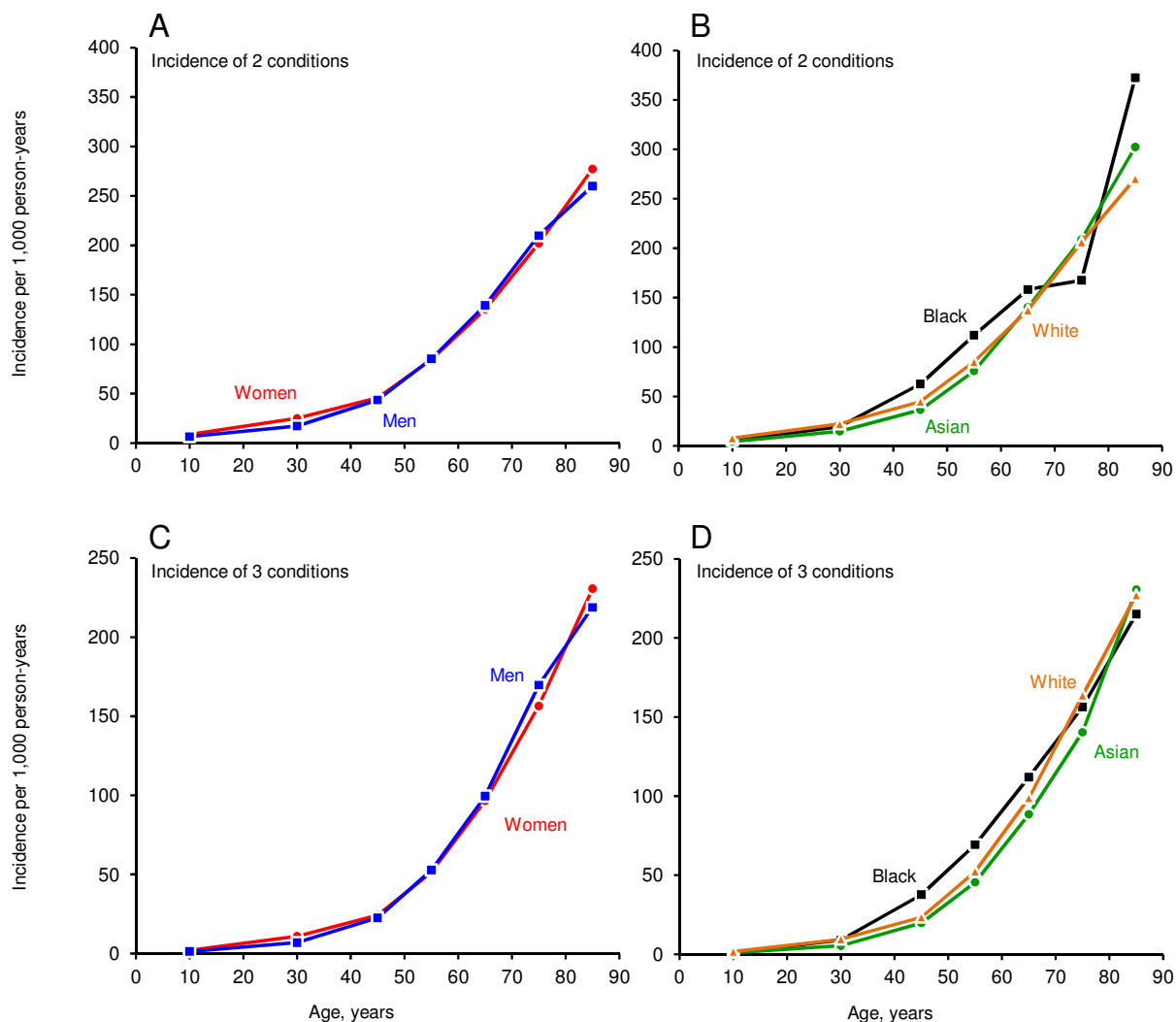


Figure 2



For peer review only

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			Women		
	Persons	Person- years	Incidence rate * (n)	Persons	Person- years	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.

BMJ Open

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

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Manuscripts

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4 1 Risk of developing multimorbidity across all ages in an historical
5
6
7 2 cohort study: differences by sex and ethnicity
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9
10 3 Jennifer L. St. Sauver *associate professor*^{1 2}, Cynthia M. Boyd *associate professor*³,
11
12 4 Brandon R. Grossardt *biostatistician*⁴, William V. Bobo *assistant professor*⁵, Lila J.
13
14 5 Finney Rutten *associate professor*^{1 2}, Véronique L. Roger *professor*^{1 2 6}, Jon O. Ebbert
15
16 6 *professor*², Terry M. Therneau *professor*⁴, Barbara P. Yawn *director of research*^{1 7},
17
18 7 Walter A. Rocca *professor*^{1 8}
19
20

21
22 8 Author Affiliations: ¹ Division of Epidemiology, Department of Health Sciences
23
24 9 Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN
25
26
27 10 55905, USA; ² The Robert D. and Patricia E. Kern Center for the Science of Health
28
29 11 Care Delivery, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN
30
31 12 55905, USA; ³ Division of Geriatric Medicine and Gerontology, School of Medicine,
32
33 13 Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287, USA; ⁴
34
35 14 Division of Biomedical Statistics and Informatics, Department of Health Sciences
36
37 15 Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN
38
39 16 55905, USA; ⁵ Department of Psychiatry and Psychology, College of Medicine, Mayo
40
41 17 Clinic, 200 First Street SW, Rochester, MN 55905, USA; ⁶ Division of Cardiovascular
42
43 18 Diseases, Department of Internal Medicine, College of Medicine, Mayo Clinic, 200 First
44
45 19 Street SW, Rochester, MN 55905, USA; ⁷ Department of Research, Olmsted Medical
46
47 20 Center, 210 Ninth Street SE, Rochester, MN 55904, USA; ⁸ Department of Neurology,
48
49 21 College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
50
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56 22 Word Count: (4,427/approximately 4,000)
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3 23 Abstract: (291/300)
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5
6 24 Strengths and limitations of this study: 219
7

8 25 References: 38
9

10 26 Figures/Tables: (5/5)
11

12 27 Supplementary Tables: 3
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17
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19 29 Corresponding Author: Walter A. Rocca, MD, MPH, Division of Epidemiology,
20
21 30 Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester,
22
23 31 MN 55905 (telephone: 507-284-3568; fax: 507-284-1516; e-mail: rocca@mayo.edu).
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30 33 Extra material supplied by the author: Supplementary tables A-C
31
32
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34

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3
4 35 **ABSTRACT**

5
6 36 Objective: To study the incidence of de novo multimorbidity across all ages in a
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8
9 37 geographically defined population with an emphasis on sex and ethnic differences.

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13 39 Design: Historical cohort study.
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18 41 Setting: All persons residing in Olmsted County, Minnesota, USA on January 1, 2000
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20 42 who had not refused permission for their records to be used for research (n = 123,716).
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25 44 Participants: We used the Rochester Epidemiology Project medical records-linkage
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27 45 system to identify all of the county residents. We identified and removed from the
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29 46 cohort all persons who had developed multimorbidity before January 1, 2000 (baseline
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31 47 date), and we followed the cohort over 14 years (January 1, 2000 through December
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33 48 31, 2013).
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39 50 Main outcome measures: Incident multimorbidity was defined as the development of
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41 51 the second of 2 conditions (dyads) from among the 20 chronic conditions selected by
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43 52 the United States Department of Health and Human Services. We also studied the
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45 53 incidence of the third of 3 conditions (triads) from among the 20 chronic conditions.
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51 55 Results: The incidence of multimorbidity increased steeply with older age; however, the
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53 56 number of people with incident multimorbidity was substantially greater in people
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55 57 younger than 65 years compared to people age 65 years or older (28,378 vs. 6,214).
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3 58 The overall risk was similar in men and women; however, the combinations of
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6 59 conditions (dyads and triads) differed extensively by age and by sex. Compared to
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8 60 Whites, the incidence of multimorbidity was higher in Blacks and lower in Asians.
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13 62 Conclusions: The risk of developing de novo multimorbidity increases steeply with older
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15 63 age, varies by ethnicity, and is similar in men and women overall. However, as
16
17 64 expected, the combinations of conditions vary extensively by age and sex. These data
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19 65 represent an important first step toward identifying the causes and the consequences of
20
21 66 multimorbidity.
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4 68 **ARTICLE SUMMARY:** Strengths and limitations of this study

5
6 69 ■ This is one of the first studies worldwide focusing on the incidence of
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8 70 multimorbidity rather than on the prevalence of multimorbidity. Prevalence
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10 71 reflects both the effect of incidence and of survival after the onset of
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12 72 multimorbidity. We used a simple definition of incident multimorbidity that can be
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14 73 replicated in other populations.
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18 74 ■ This study covered an entire geographically defined population, and used a
19
20 75 unique records-linkage system. Persons were followed historically over 14
21
22 76 years. None of the data were derived from self-report or interviews.
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25 77 ■ Studies of multimorbidity require the definition of the number of conditions
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27 78 considered, of the time window of occurrence, and of the source of data (medical
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29 79 records vs. interview). We used the 20 conditions recommended by the United
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31 80 States Department of Health and Human Services. These 20 conditions
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33 81 represent a first consensus list; however, not all of the conditions have the same
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35 82 impact on the complexity of care or on the quality of life of patients.
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39 83 ■ Potential limitations of this study include the uncertain validity of diagnostic
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41 84 codes, the possible incompleteness of information due to in or out migration, and
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43 85 the inability to generalize our findings to other populations with different
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45 86 demographic or social characteristics.
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49 87 ■ Replication of this study in other populations in the United States and worldwide
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51 88 will allow for useful comparisons.
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90 INTRODUCTION

91 The demographic expansion of the elderly population and the improvements in survival
92 of people affected by chronic conditions have caused a dramatic rise in the number of
93 people living with multimorbidity (≥ 2 chronic conditions). In the United States, the
94 prevalence of multimorbidity among Medicare recipients increases from 62% at age 65 -
95 74 years to 82% at ages 85 years and older.¹ The monetary costs associated with
96 managing patients with multiple chronic conditions are overwhelming.²⁻⁴ In addition,
97 fragmented health care in patients with multimorbidity causes a particularly high risk for
98 complications and a lower quality of life.^{5,6}

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

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

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3 113 public health priority for the nation.¹⁵ The Rochester Epidemiology Project (REP)
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5 114 medical records-linkage system captures long-term medical information on a stable
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8 115 population, and is therefore uniquely positioned to study the incidence of multimorbidity.
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10 116 In a previous paper, we described in detail the patterns of prevalent multimorbidity in
11
12 117 this population.¹⁶ In this study, we further leveraged this data resource to examine the
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14 118 incidence of multimorbidity across all ages, separately in men and women, and in three
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16
17 119 ethnic groups.¹⁷
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21 22 121 METHODS

23 24 25 122 Study population

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28 123 The REP has tracked and linked health care information for the population of Olmsted
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30 124 County, MN, since 1966.¹⁷⁻¹⁹ The vast majority of medical care in this community is
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32 125 currently provided by a few health care institutions: Olmsted Medical Center and its
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34 126 affiliated hospital, Mayo Clinic and its two affiliated hospitals, the Rochester Family
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36 127 Medicine Clinic, and a few smaller care facilities. The health care records from these
37
38 128 institutions are linked together through the REP records-linkage system.¹⁷⁻¹⁹ Persons
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40 129 are considered residents of Olmsted County at the time of each health care visit based
41
42 130 on their address. Over the years, this address information has been accumulated and
43
44 131 is used to define who resided in Olmsted County at any given point in time since 1966
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46 132 (REP Census). The population counts obtained by the REP Census are similar to those
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48 133 obtained by the US Census, indicating that virtually the entire population of the county is
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50 134 captured by the system.¹⁸⁻²⁰ We used the REP Census to identify all individuals who
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54 135 resided in Olmsted County on January 1, 2000 (baseline date); however, we included
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3 136 only individuals who had not refused permission to use their medical records for
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6 137 research (Minnesota research authorization).^{18,21,22}
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10 139 Definition of incident multimorbidity

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13 140 We focused on 20 selected chronic conditions recommended by the US-DHHS for
14
15 141 studying multimorbidity.^{23,24} The list of the 20 conditions and the corresponding ICD-9
16
17 142 codes used in this study are provided in Supplementary Table A.^{23,24} We first identified
18
19 143 all ICD-9 codes associated with these 20 chronic conditions that occurred in the
20
21 144 population between January 1, 1995 and December 31, 1999 (5 years before the
22
23 145 baseline date, January 1, 2000). Persons who did not have any ICD-9 code for a given
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25 146 condition were assumed to not have the condition of interest. By contrast, residents
26
27 147 were defined as having a chronic condition if they had at least two ICD-9 codes for that
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29 148 condition separated by more than 30 days, and the incidence date was assigned at the
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31 149 time they received a second diagnostic code.
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37 150 Persons who had 2 or more of the 20 conditions at baseline were considered to
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39 151 have prevalent multimorbidity and were therefore excluded from incidence analyses of 2
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41 152 chronic conditions (dyads). Similarly, persons who had 3 or more of the 20 conditions
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43 153 at baseline were excluded from incidence analyses of 3 chronic conditions (triads). All
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45 154 persons in this fixed population cohort were followed historically through the REP
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47 155 records-linkage system for approximately 14 years to study the emergence of new
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49 156 conditions.
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55 158 Statistical Analyses

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3 159 All persons in the cohort were followed from January 1, 2000 through the last contact
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6 160 with the records-linkage system (the earliest of death date, last medical visit date, or
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8 161 December 31, 2013). The incidence of each of the 20 chronic conditions was
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10 162 calculated among persons free of that condition at baseline. Persons contributed
11
12 163 person-years to the denominator for the incidence of 2 conditions (development of a
13
14 164 second condition in a dyad) only during the time when they had 0 or 1 chronic
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16 165 conditions, whereas persons contributed person-years to the denominator for the
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18 166 incidence of 3 chronic conditions (development of a third condition in a triad) only when
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20 167 they had 0, 1, or 2 chronic conditions. Although the majority of people accumulated
21
22 168 conditions one-at-a-time, some subjects jumped from 0 to 2 conditions, or from 1 to 3,
23
24 169 or even from 0 to 3 conditions. For example, a person previously considered free of all
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26 170 of the 20 conditions who was diagnosed with hyperlipidemia, hypertension, and
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28 171 depression during one visit was counted as having three incident dyads and one
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30 172 incident triad on the same date.
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36 173 Incidence rates were reported separately by age (using seven age strata or
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38 174 splitting the entire population in 0-64 and ≥ 65 years), sex, and ethnicity, and were
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40 175 directly standardized by age and sex to the total US 2010 Decennial Census after
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42 176 removing projected prevalence (see Supplementary Table B). Because the study
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44 177 covered the target population completely, and no sampling was involved, confidence
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46 178 intervals were not included in the tables.^{25,26} Ethnicity data were not available for 9,176
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48 179 people (7.4% of the cohort). These individuals were included in the overall and age-
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50 180 and sex-specific analyses, but not in the ethnicity-specific analyses.
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3 181 Although the 20 conditions proposed by the US-DHHS represent a national
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5 182 consensus,¹⁵ some of the conditions may have a different prognostic impact than
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8 183 others. For example, hyperlipidemia and hypertension often occur together and tend to
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10 184 remain asymptomatic. Therefore, we performed a set of sensitivity analyses combining
11
12 185 hyperlipidemia and hypertension as a single chronic condition. The date of incidence
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14 186 for the single chronic condition of hyperlipidemia and/or hypertension was defined as
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16 187 the date the person first met criteria for either of these conditions.
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21 22 189 RESULTS

23 24 25 190 Description of the Olmsted County population

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28 191 The REP Census identified 129,311 Olmsted County, MN residents on January 1, 2000
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30 192 compared with 124,277 individuals counted by the 2000 US Census (104.1%); 123,716
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32 193 persons provided Minnesota research authorization for medical record research (95.7%)
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34 194 and were included in our analyses. A total of 17,655 people (14.3%) had 2 or more
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36 195 conditions at the baseline date and 9,368 (7.6%) had 3 or more conditions (prevalent
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38 196 multimorbidity). Overall, we observed a total of 1,334,906 person-years of follow-up;
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40 197 however, as expected, the length of follow-up varied by age group. For example,
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42 198 median follow-up was 13.1 years in persons aged 0 to 19 years at baseline, 12.3 years
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44 199 in persons aged 70 to 79 years at baseline, and 4.9 years in persons aged 80 years or
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46 200 older at baseline.
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52 201 Figure 1 and Supplementary Table C report the incidence of each of the 20
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54 202 chronic conditions considered separately by age and sex. The incidence of most of the
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56 203 chronic conditions increased steeply with older age. However, the incidence of asthma,
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3 204 substance abuse disorders, hepatitis, autism spectrum disorder, and infection with
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5 205 human immunodeficiency virus was higher in the younger population compared to
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8 206 persons older than 60 years. The incidence of depression increased from ages 0-19 to
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10 207 20-39 years, declined from 40-49 to 60-69 years, and increased sharply again
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12 208 thereafter. The incidence of most conditions was higher in men compared to women of
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14 209 the same age; however, women had a higher incidence of depression, arthritis, asthma,
15
16 210 and osteoporosis. The incidence curves in men and women crossed at age 50-59
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18 211 years for cancer and at age 60-69 years for chronic obstructive pulmonary disease
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20 212 (Figure 1).
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27 214 Incidence of multimorbidity by age, sex, and ethnicity

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30 215 Figure 2 shows the age-specific incidence rates of multimorbidity in men and women
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32 216 separately (panels A and C), and in three ethnic groups (panels B and D). Both the
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34 217 incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased
35
36 218 steeply with older age (Table 1, Table 2, and Figure 2). For example, the incidence of 2
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38 219 chronic conditions in men was 6.5/1,000 person-years in persons who were ages 0-19
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40 220 years, and 260.0/1,000 in persons who were ≥ 80 years. The overall incidence of 2
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42 221 chronic conditions was slightly higher in women compared to men (overall standardized
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44 222 incidence rates 38.8 vs. 35.5/1,000 person-years; Table 1). The incidence of 2 chronic
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46 223 conditions was higher in Blacks compared to Whites, but lower in Asians compared to
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48 224 Whites (see standardized incidence rates in Table 1 and Figure 2). We observed
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50 225 similar patterns for the development of 3 chronic conditions (see standardized incidence
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52 226 rates in Table 2 and Figure 2). The overall incidence of 3 conditions was similar in men
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3 227 and women (standardized incidence rates 25.5/1,000 person-years in men vs.
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5 228 26.6/1,000 person-years in women); however, it was higher in Blacks and lower in
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8 229 Asians, compared to Whites (Figure 2).
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10 230 In the set of sensitivity analyses in which we combined hyperlipidemia and
11
12 231 hypertension as a single condition, we observed a slight decrease in the incidence of 2
13
14 232 chronic conditions and of 3 chronic conditions compared with the primary analyses.
15
16 233 The overall incidence rate of 2 conditions decreased from 35.0 to 34.0/1,000 person-
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18 234 years in men and from 40.3 to 40.0/1,000 person-years in women. The incidence rate
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20 235 of 3 conditions decreased from 24.7 to 22.5/1,000 person-years in men and from 28.5 to
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22 236 27.0/1,000 person-years in women (incidence rates non-standardized; data not shown
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24 237 in the Tables). For both 2 and 3 conditions, the decrease in incidence was more
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26 238 sizeable in men than in women.
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34 240 Incidence of dyads and triads

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37 241 Table 3 shows the incidence of the most common dyads or triads of chronic conditions
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39 242 in seven age strata and for men and women separately. As expected, the incidence of
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41 243 dyads and triads varied extensively with age. For example, the most common incident
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43 244 dyad in persons 0-19 years was depression and asthma (1.8/1,000 person-years in
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45 245 boys or men and 2.9/1,000 person-years in girls or women). By comparison, the most
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47 246 common dyad in persons ≥ 80 years was hypertension and cancer in men (18.9/1,000
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49 247 person-years) and hypertension and arthritis in women (27.7/1,000 person-years).
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51 248 Similarly, the most common incident triad of conditions in persons aged 0-19 years was
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53 249 depression, asthma, and substance abuse disorders in both sexes. By comparison, the
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3 250 most common incident triads in persons ≥ 80 years were hypertension, cancer, and
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6 251 arrhythmia in men and hyperlipidemia, hypertension, and arthritis in women.

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8 252 As expected, the incidence of dyads and triads also varied by sex. In some
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10 253 instances, the composition of the dyads or triads was the same for men and women, but
11
12 254 the magnitude of the incidence rate was different. In other instances, the magnitude of
13
14 255 the incidence rate was similar in men and women, but the composition of the dyads and
15
16 256 triads varied by sex. For example, the most common incident dyad in persons aged 60-
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18 257 69 years was hyperlipidemia and hypertension in both sexes, but the incidence rate was
19
20 258 higher in men compared to women (23.4/1,000 person-years vs. 18.8/1,000 person-
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22 259 years). By contrast, the incidence rates of the most common triads in persons aged 60-
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24 260 69 years were similar in men and women (11.6/1,000 vs. 10.3/1,000 person-years);
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26 261 however, they included different conditions (Table 3).
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33 34 263 DISCUSSION

35 36 37 264 Statement of the principal findings

38
39 265 The burden of multimorbidity in the United States is high and is increasing with an aging
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41 266 population and with improvements in survival. We leveraged a unique longitudinal data
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43 267 resource covering an entire, stable, and geographically defined population to examine
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45 268 the incidence of multimorbidity across all ages. The incidence of 2 chronic conditions
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47 269 and the incidence of 3 chronic conditions increased steeply with older age, and the
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49 270 overall risk was similar in men and women. However, the number of people who
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51 271 developed multimorbidity before age 65 was more than four times greater than the
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53 272 number of people who developed multimorbidity after age 65. The incidence of
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3 273 multimorbidity was highest in Blacks, and lowest in Asians. Finally, as expected, the
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5 274 combinations of conditions in incident dyads and triads differed extensively by age and
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8 275 by sex. These results have important implications for identifying individuals at higher
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10 276 risk of developing multimorbidity at different ages. These data are also a first step
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12 277 toward understanding the causes and the consequences of multimorbidity.
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17 279 Strengths and limitations

20 280 A unique strength of our study was the ability to measure the incidence of multimorbidity
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22 281 documented in medical records across seven age groups and for an entire,
23
24 282 geographically defined population. We used historical data both to exclude individuals
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26 283 with prevalent multimorbidity at baseline and to follow individuals over a long period of
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28 284 time to accurately document the development of incident multimorbidity. In total, our
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30 285 findings reflect 19 years of data accumulation (5 years before and 14 years after the
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32 286 baseline date).
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37 287 Unfortunately, there is no standard definition of multimorbidity. Previous studies
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39 288 have included a wide range of chronic conditions and a wide range of time frames. We
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41 289 defined multimorbidity using the 20 conditions selected by US-DHHS which were
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43 290 chosen because they “meet the definition for chronicity, are prevalent [common], and
44
45 291 are potentially amenable to public health or clinical interventions or both.”²³ However,
46
47 292 this definition provides equal weight to each of the 20 conditions without considering the
48
49 293 impact of combinations of specific conditions on the quality of life of patients, the
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51 294 complexity of their joint management, and the severity of their long-term outcomes. In
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54 295 addition, this list does not include a number of conditions that may have a significant
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3 296 impact on the burden of multimorbidity in older subjects (e.g., hearing and vision
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6 297 problems). Such conditions should be considered in future studies of multimorbidity.
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8 298 By contrast, the list includes some conditions that were less common in the general
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10 299 population. For example, autism appeared as part of an incident dyad in only 31
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12 300 persons, and HIV infection in only 41 persons. Therefore, further efforts are needed to
13
14 301 refine the list of the most relevant conditions to study multimorbidity, recognizing that
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16 302 the most relevant conditions will vary depending on the age and sex of the population.
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20 303 Some of the dyads and triads derived by the combination of the 20 conditions
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22 304 selected by the US-DHHS may have a much stronger impact on the complexity of
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24 305 clinical management than others.²⁷ Therefore, some dyads or triads may be
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26 306 particularly costly for the health system, harder for the patient to manage by
27
28 307 themselves, less amenable to a single disease approach to care (e.g., telemonitoring for
29
30 308 heart failure), and may have a stronger effect on functionality, severity of symptoms,
31
32 309 and risk of death. In addition, social factors (e.g., inadequate insurance, low education)
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34 310 and behavioral factors (e.g., poor diet) not reflected in the list of 20 US-DHHS
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36 311 conditions may be as important, or more important, than the 20 conditions in
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38 312 determining the complexity of clinical management and long-term outcomes.²⁷
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43 313 For example, because hyperlipidemia and hypertension are typically
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45 314 asymptomatic, and are often diagnosed as the result of routine screening, their
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47 315 combination is likely to have a much lower impact on the life of the patient than the
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49 316 combination of schizophrenia and heart failure. However, both combinations are
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51 317 considered multimorbidity by the US-DHHS definition. Our sensitivity analyses highlight
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53 318 this problem. As expected, when hyperlipidemia and hypertension were considered as
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3 319 a single condition, the overall incidence of multimorbidity decreased. The decreases
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6 320 were relatively small but were more sizeable in men than in women. These findings
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8 321 emphasize the importance of reaching consensus on the list of conditions to be used to
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10 322 define multimorbidity. However, it is difficult to assess the utility of the 20 conditions
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12 323 included in the US-DHHS list without also understanding how different combinations of
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14 324 these conditions impact long term outcomes. Therefore, we plan to continue this initial
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16 325 incidence study with further analyses to assess which combinations of conditions have
17
18 326 the greatest impact on adverse outcomes, including patient quality of life and complexity
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20 327 of clinical management.²⁷

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22 328 We defined incident multimorbidity as the date on which a person met the criteria
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24 329 for a second condition or for a third condition. We used an approach similar to that
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26 330 used in the definition for the onset of metabolic syndrome (reaching three of five
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28 331 components of the syndrome).^{28,29} This simple operational definition of incident
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30 332 multimorbidity should be easy to replicate, and should facilitate future comparisons with
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32 333 other populations.

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34 334 Potential limitations of our study include the inability to validate the ICD-9 codes.
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36 335 It was not possible to confirm all diagnoses for the entire study population, and some
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38 336 ICD-9 codes may have been assigned in error (e.g., “rule out” diagnostic codes). To
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40 337 reduce the likelihood of a single ICD-9 code error, we required two or more diagnosis
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42 338 codes separated by more than 30 days for a person to be defined as having a condition.
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44 339³⁰ However, if a person received a valid code and was lost to follow-up or died rapidly
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46 340 after diagnosis, we may have underestimated the incidence of some of the conditions.
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3 341 In addition, we used diagnosis date as a proxy for the true date of onset of the
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5 342 condition.

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8 343 Some individuals may have moved into Olmsted County after having been
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10 344 diagnosed with one or more chronic conditions elsewhere. If those persons continued
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12 345 to receive care within the REP for a number of years, we captured their chronic
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14 346 condition at the time of subsequent health care visits. However, we did not know the
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16 347 true date of onset for the condition, and the sequence of accumulation of conditions
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18 348 could be distorted. Because the population of Olmsted County is stable, particularly
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20 349 among persons who are 40 years of age or older,¹⁹ we do not expect a major distortion
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22 350 of the multimorbidity incidence rates observed in this study due to migration.
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27 351 Finally, our study focused on a single geographically defined US population, and
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29 352 the incidence of multimorbidity may differ in other populations. However, the
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31 353 demographic and socioeconomic characteristics of our population are similar to those of
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33 354 the upper Midwest of the United States,²⁰ and the prevalence of multimorbidity in
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35 355 persons 65 years of age or older was similar in our population compared with the entire
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37 356 US Medicare population.¹⁶ Replication of this study in other populations in the United
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39 357 States and worldwide will allow for useful comparisons.³¹
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46 359 Comparison with other studies

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49 360 A number of studies have described the prevalence of multimorbidity in various
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51 361 populations;^{1,7-12} however, few studies have described the incidence of multimorbidity,
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53 362 and no incidence studies are available for the US. In 1998, Van den Akker and
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55 363 colleagues estimated the one year incidence of multimorbidity in patients from a
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3 364 network of family practices in the Netherlands.³² Incident multimorbidity was defined as
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5 365 the new development of at least 2 of 335 diagnostic categories within a one year period.
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8 366 Overall, 7.9% of their population developed one new disease and 1.3% developed two
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10 367 or more new diseases in one year. The proportion of people who developed two or
11
12 368 more new conditions increased with older age, but did not differ substantially by sex. It
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15 369 is difficult to compare our results directly to the Dutch findings because of
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17 370 methodological differences (e.g., number of conditions considered and time frame), and
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20 371 because it is not clear whether some of the participants in the Dutch study already had
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22 372 one or more conditions at baseline. However, we observed similar patterns of
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24 373 increasing incidence with older age, and limited differences between men and women in
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27 374 overall incidence.

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29 375 More recently, Melis and colleagues assessed the incidence of multimorbidity in
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31 376 Swedish people aged 75 years or older at baseline who participated in a longitudinal
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33 377 cohort study.³³ Incident multimorbidity was defined as the development of at least 2 of
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36 378 39 chronic conditions during three years of follow-up. Participants with none of the 39
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38 379 chronic conditions at baseline had a multimorbidity incidence rate of 12.6 per 100
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40 380 person-years, and patients with one of the 39 conditions at baseline had an incidence
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42 381 rate of 32.9 per 100 person-years. Although we examined fewer conditions than the
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44 382 Swedish group (20 vs. 39), and the ascertainment of incident conditions was different
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46 383 (medical records data vs. survey methods), our incidence rates of multimorbidity in
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48 384 subjects aged 75 years or older were similar (19.1 per 100 person-years in people with
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50 385 no conditions at baseline and 38.9 per 100 person-years in persons with one condition
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53 386 at baseline; both sexes combined; data not shown).

387

388 **Meaning of the study**

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

402 Prior studies of the prevalence of multimorbidity have shown a dramatic increase
403 in the number of people living with 2 or more chronic conditions at older ages.^{1,7-11}
404 However, the high prevalence of multimorbidity in the older population implies that
405 relatively few older individuals remain at risk of developing multimorbidity. Overall,
406 among persons aged 80 years or older at baseline, only 891 out of 3,710 (24.0%) were
407 at risk of developing 2 chronic conditions (the other 76.0% already had 2 or more of the
408 20 conditions). Although the persons who reached 80 years of age or older and

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3 409 remained free of multimorbidity were a particularly resilient group, they had a higher risk
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6 410 of developing subsequent multimorbidity than younger persons.
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8 411 We also found that the total number of people who developed multimorbidity
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10 412 before age 65 years was more than 4 times greater than the number of people who
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12 413 developed multimorbidity at ages 65 or older (28,378 vs. 6,214). These data emphasize
14
15 414 the need to target preventive efforts at much younger ages, but represent only a first
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17 415 step toward future research to identify the social, behavioral, and clinical risk and
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20 416 protective factors for multimorbidity.
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22 417 We found important differences in the incidence of multimorbidity by ethnicity.
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24 418 The age standardized incidence rates of multimorbidity were higher in Blacks and lower
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27 419 in Asians compared to Whites. Our findings are consistent with previous studies that
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29 420 showed a higher prevalence of multimorbidity in Blacks compared to Whites, but a lower
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31 421 prevalence of multimorbidity in Asians.^{8,16,36-38} Our data suggest that some of these
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33 422 differences in prevalence may be attributed to differences in the incidence of the
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36 423 conditions among different ethnic groups. However, differential survival may also
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38 424 contribute to the differences in prevalence. In turn, both differences in incidence and in
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40 425 prevalence may be influenced by socioeconomic factors, lifestyle behaviors, social
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43 426 environment, and healthcare access. Further research is needed to better characterize
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46 427 these disparities and to identify the causal mechanisms that contribute to different
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48 428 development of chronic conditions and to different survival.
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50 429 As expected, the incidence and the composition of the dyads and triads of
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52 430 conditions varied extensively across age and sex strata. For example, women 20 years
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55 431 of age or older were more likely to have depression as a component of their incident
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3 432 multimorbidity dyads and triads compared to men. Such differences may lead to
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6 433 different long-term outcomes in men and women. Therefore, these data are useful to
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8 434 understand how multimorbidity develops, and are an important first step toward future
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10 435 research. In particular, such incident data are necessary to study the chronological
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12 436 order of acquisition of multiple chronic conditions in different age, sex, and ethnic strata.
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15 437 Incidence data are also necessary to determine whether the differential order of
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17 438 acquisition is associated with a different risk of adverse long-term outcomes such as
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19 439 hospitalizations, emergency department visits, or death. For example, it is not clear
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21 440 whether acquiring depression prior to arthritis results in worse long-term outcomes
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23 441 compared with acquiring arthritis prior to depression. Future studies are also needed to
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25 442 understand how additional chronic conditions accumulate after the development of a
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27 443 second and third condition. Finally, the incidence of specific dyads and triads reflects
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29 444 the incidence of the individual conditions in specific age and sex groups. Many of these
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31 445 dyads and triads are expected to develop simply by chance. Therefore, future studies
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33 446 are needed to identify the dyads and triads that co-occur beyond chance. Identification
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35 447 of incident dyads and triads that reflect shared etiologic mechanisms or shared risk
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37 448 factors may lead to combined treatment or prevention strategies.
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46 450 Conclusions and clinical implications

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49 451 It is important and urgent to understand the causes and the consequences of
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51 452 multimorbidity to inform efforts to delay and prevent disease onset and to develop
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53 453 effective strategies for caring for patients with multimorbidity. We studied the incidence
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55 454 of multimorbidity across all ages, separately in men and women, and in three ethnic
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3 455 groups in a geographically defined US population. The incidence of multimorbidity
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6 456 increased steeply with older age and was higher in Blacks but lower in Asians
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8 457 compared to Whites. Men and women had a similar overall risk, but the combinations
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10 458 of conditions within dyads and triads varied extensively by age and by sex. These data
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12 459 represent an important first step toward identifying conditions which co-occur more
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14 460 frequently than chance alone, identifying specific risk factors for multimorbidity,
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16 461 understanding how chronic conditions accumulate over time, and toward identifying
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18 462 combinations of conditions that predict adverse outcomes.
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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.

Ethnicity age (years)	Men			Women		
	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).

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4 1 **Risk of developing multimorbidity across all ages in an**
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7 2 **historical cohort study: differences by sex and ethnicity**
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10 3 Jennifer L. St. Sauver *associate professor*^{1 2}, Cynthia M. Boyd *associate professor*³,
11 4 Brandon R. Grossardt *biostatistician*⁴, William V. Bobo *assistant professor*⁵, Lila J.
12 5 Finney Rutten *associate professor*^{1 2}, Véronique L. Roger *professor*^{1 2 6}, Jon O. Ebbert
13 6 *professor*², Terry M. Therneau *professor*⁴, Barbara P. Yawn *director of research*^{1 7},
14 7 Walter A. Rocca *professor*^{1 8}
15
16
17
18
19
20
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22
23
24
25

26 9 **Author Affiliations:** ¹ Division of Epidemiology, Department of Health Sciences
27
28 10 Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN
29
30 11 55905, USA; ² The Robert D. and Patricia E. Kern Center for the Science of Health
31
32 12 Care Delivery, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN
33
34 13 55905, USA; ³ Division of Geriatric Medicine and Gerontology, School of Medicine,
35
36 14 Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287, USA; ⁴
37
38 15 Division of Biomedical Statistics and Informatics, Department of Health Sciences
39
40 16 Research, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN
41
42 17 55905, USA; ⁵ Department of Psychiatry and Psychology, College of Medicine, Mayo
43
44 18 Clinic, 200 First Street SW, Rochester, MN 55905, USA; ⁶ Division of Cardiovascular
45
46 19 Diseases, Department of Internal Medicine, College of Medicine, Mayo Clinic, 200 First
47
48 20 Street SW, Rochester, MN 55905, USA; ⁷ Department of Research, Olmsted Medical
49
50 21 Center, 210 Ninth Street SE, Rochester, MN 55904, USA; ⁸ Department of Neurology,
51
52 22 College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
53
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3 23 **Word Count:** (4,427/approximately 4,000)
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20

21 30 **Corresponding Author:** Walter A. Rocca, MD, MPH, Division of Epidemiology,
22
23 Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester,
24 31
25 MN 55905 (telephone: 507-284-3568; fax: 507-284-1516; e-mail: rocca@mayo.edu).
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32 34 Extra material supplied by the author: Supplementary tables A-C
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4 36 **ABSTRACT**

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6 37 **Objective:** To study the incidence of de novo multimorbidity across all ages in a
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9 38 geographically defined population with an emphasis on sex and ethnic differences.

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13 40 **Design:** Historical cohort study.
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18 42 **Setting:** All persons residing in Olmsted County, Minnesota, USA on January 1, 2000
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20 43 who had not refused permission for their records to be used for research (n = 123,716).
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25 45 **Participants:** We used the Rochester Epidemiology Project medical records-linkage
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27 46 system to identify all of the county residents. We identified and removed from the
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29 47 cohort all persons who had developed multimorbidity before January 1, 2000 (baseline
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31 48 date), and we followed the cohort over 14 years (January 1, 2000 through December
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33 49 31, 2013).
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39 51 **Main outcome measures:** Incident multimorbidity was defined as the development of
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41 52 the second of 2 conditions (dyads) from among the 20 chronic conditions selected by
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43 53 the United States Department of Health and Human Services. We also studied the
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45 54 incidence of the third of 3 conditions (triads) from among the 20 chronic conditions.
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51 56 **Results:** The incidence of multimorbidity increased steeply with older age; however, the
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53 57 number of people with incident multimorbidity was substantially greater in people
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55 58 younger than 65 years compared to people age 65 years or older (28,378 vs. 6,214).
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3 59 The overall risk was similar in men and women; however, the combinations of
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6 60 conditions (dyads and triads) differed extensively by age and by sex. Compared to
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8 61 Whites, the incidence of multimorbidity was higher in Blacks and lower in Asians.
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12 63 **Conclusions:** The risk of developing de novo multimorbidity increases steeply with
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15 64 older age, varies by ethnicity, and is similar in men and women overall. However, **as**
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17 65 **expected**, the combinations of conditions vary extensively by age and sex. These data
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20 66 represent an important first step toward identifying the causes and the consequences of
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22 67 multimorbidity.
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69 **ARTICLE SUMMARY: Strengths and limitations of this study**

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

91 INTRODUCTION

92 The demographic expansion of the elderly population and the improvements in survival
93 of people affected by chronic conditions have caused a dramatic rise in the number of
94 people living with multimorbidity (≥ 2 chronic conditions). In the United States, the
95 prevalence of multimorbidity among Medicare recipients increases from 62% at age 65 -
96 74 years to 82% at ages 85 years and older.¹ The monetary costs associated with
97 managing patients with multiple chronic conditions are overwhelming.²⁻⁴ In addition,
98 fragmented health care in patients with multimorbidity causes a particularly high risk for
99 complications and a lower quality of life.^{5,6}

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

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

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3 114 public health priority for the nation.¹⁵ The Rochester Epidemiology Project (REP)
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5 115 medical records-linkage system captures long-term medical information on a stable
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8 116 population, and is therefore uniquely positioned to study the incidence of multimorbidity.
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10 117 In a previous paper, we described in detail the patterns of prevalent multimorbidity in
11
12 118 this population.¹⁶ In this study, we further leveraged this data resource to examine the
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14 119 incidence of multimorbidity across all ages, separately in men and women, and in three
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17 120 ethnic groups.¹⁷
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22 122 **METHODS**

25 123 **Study population**

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28 124 The REP has tracked and linked health care information for the population of Olmsted
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30 125 County, MN, since 1966.¹⁷⁻¹⁹ The vast majority of medical care in this community is
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32 126 currently provided by a few health care institutions: Olmsted Medical Center and its
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34 127 affiliated hospital, Mayo Clinic and its two affiliated hospitals, the Rochester Family
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36 128 Medicine Clinic, and a few smaller care facilities. The health care records from these
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38 129 institutions are linked together through the REP records-linkage system.¹⁷⁻¹⁹ Persons
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40 130 are considered residents of Olmsted County at the time of each health care visit based
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42 131 on their address. Over the years, this address information has been accumulated and
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44 132 is used to define who resided in Olmsted County at any given point in time since 1966
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46 133 (REP Census). The population counts obtained by the REP Census are similar to those
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48 134 obtained by the US Census, indicating that virtually the entire population of the county is
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50 135 captured by the system.¹⁸⁻²⁰ We used the REP Census to identify all individuals who
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52 136 resided in Olmsted County on January 1, 2000 (baseline date); however, we included
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3 137 only individuals who had not refused permission to use their medical records for
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5 138 research (Minnesota research authorization).^{18,21,22}
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10 140 **Definition of incident multimorbidity**

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13 141 We focused on 20 selected chronic conditions recommended by the US-DHHS for
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15 142 studying multimorbidity.^{23,24} The list of the 20 conditions and the corresponding ICD-9
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17 143 codes used in this study are provided in Supplementary Table A.^{23,24} We first identified
18
19 144 all ICD-9 codes associated with these 20 chronic conditions that occurred in the
20
21 145 population between January 1, 1995 and December 31, 1999 (5 years before the
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23 146 baseline date, January 1, 2000). Persons who did not have any ICD-9 code for a given
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25 147 condition were assumed to not have the condition of interest. By contrast, residents
26
27 148 were defined as having a chronic condition if they had at least two ICD-9 codes for that
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29 149 condition separated by more than 30 days, and the incidence date was assigned at the
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31 150 time they received a second diagnostic code.
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37 151 Persons who had 2 or more of the 20 conditions at baseline were considered to
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39 152 have prevalent multimorbidity and were therefore excluded from incidence analyses of 2
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41 153 chronic conditions (dyads). Similarly, persons who had 3 or more of the 20 conditions
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43 154 at baseline were excluded from incidence analyses of 3 chronic conditions (triads). All
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45 155 persons in this fixed population cohort were followed historically through the REP
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47 156 records-linkage system for approximately 14 years to study the emergence of new
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49 157 conditions.
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55 158 56 159 **Statistical Analyses**

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3 160 All persons in the cohort were followed from January 1, 2000 through the last contact
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5 161 with the records-linkage system (the earliest of death date, last medical visit date, or
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7 162 December 31, 2013). The incidence of each of the 20 chronic conditions was
8
9 163 calculated among persons free of that condition at baseline. Persons contributed
10
11 164 person-years to the denominator for the incidence of 2 conditions (development of a
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13 165 second condition in a dyad) only during the time when they had 0 or 1 chronic
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15 166 conditions, whereas persons contributed person-years to the denominator for the
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17 167 incidence of 3 chronic conditions (development of a third condition in a triad) only when
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19 168 they had 0, 1, or 2 chronic conditions. Although the majority of people accumulated
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21 169 conditions one-at-a-time, some subjects jumped from 0 to 2 conditions, or from 1 to 3,
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23 170 or even from 0 to 3 conditions. For example, a person previously considered free of all
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25 171 of the 20 conditions who was diagnosed with hyperlipidemia, hypertension, and
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27 172 depression during one visit was counted as having three incident dyads and one
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29 173 incident triad on the same date.

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32 174 Incidence rates were reported separately by age (using seven age strata or
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34 175 splitting the entire population in 0-64 and ≥ 65 years), sex, and ethnicity, and were
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36 176 directly standardized by age and sex to the total US 2010 Decennial Census after
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38 177 removing projected prevalence (see Supplementary Table B). Because the study
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40 178 covered the target population completely, and no sampling was involved, confidence
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42 179 intervals were not included in the tables.^{25,26} Ethnicity data were not available for 9,176
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44 180 people (7.4% of the cohort). These individuals were included in the overall and age-
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46 181 and sex-specific analyses, but not in the ethnicity-specific analyses.

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3 182 Although the 20 conditions proposed by the US-DHHS represent a national
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5 183 consensus,¹⁵ some of the conditions may have a different prognostic impact than
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8 184 others. For example, hyperlipidemia and hypertension often occur together and tend to
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10 185 remain asymptomatic. Therefore, we performed a set of sensitivity analyses combining
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12 186 hyperlipidemia and hypertension as a single chronic condition. The date of incidence
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14 187 for the single chronic condition of hyperlipidemia and/or hypertension was defined as
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16 188 the date the person first met criteria for either of these conditions.
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21 22 190 **RESULTS**

23 24 25 191 **Description of the Olmsted County population**

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28 192 The REP Census identified 129,311 Olmsted County, MN residents on January 1, 2000
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30 193 compared with 124,277 individuals counted by the 2000 US Census (104.1%); 123,716
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32 194 persons provided Minnesota research authorization for medical record research (95.7%)
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34 195 and were included in our analyses. A total of 17,655 people (14.3%) had 2 or more
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36 196 conditions at the baseline date and 9,368 (7.6%) had 3 or more conditions (prevalent
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38 197 multimorbidity). Overall, we observed a total of 1,334,906 person-years of follow-up;
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40 198 **however, as expected**, the length of follow-up varied by age group. For example,
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42 199 median follow-up was 13.1 years in persons aged 0 to 19 years at baseline, 12.3 years
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44 200 in persons aged 70 to 79 years at baseline, and 4.9 years in persons aged 80 years or
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46 201 older at baseline.
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52 202 Figure 1 and Supplementary Table C report the incidence of each of the 20
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54 203 chronic conditions considered separately by age and sex. The incidence of most of the
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56 204 chronic conditions increased steeply with older age. However, the incidence of asthma,
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3 205 substance abuse disorders, hepatitis, autism spectrum disorder, and infection with
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5 206 human immunodeficiency virus was higher in the younger population compared to
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8 207 persons older than 60 years. The incidence of depression increased from ages 0-19 to
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10 208 20-39 years, declined from 40-49 to 60-69 years, and increased sharply again
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12 209 thereafter. The incidence of most conditions was higher in men compared to women of
13
14 210 the same age; however, women had a higher incidence of depression, arthritis, asthma,
15
16 211 and osteoporosis. The incidence curves in men and women crossed at age 50-59
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18 212 years for cancer and at age 60-69 years for chronic obstructive pulmonary disease
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20 213 (Figure 1).
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27 215 **Incidence of multimorbidity by age, sex, and ethnicity**

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30 216 Figure 2 shows the age-specific incidence rates of multimorbidity in men and women
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32 217 separately (panels A and C), and in three ethnic groups (panels B and D). Both the
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34 218 incidence of 2 chronic conditions and the incidence of 3 chronic conditions increased
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36 219 steeply with older age (Table 1, Table 2, and Figure 2). For example, the incidence of 2
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38 220 chronic conditions in men was 6.5/1,000 person-years in persons who were ages 0-19
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40 221 years, and 260.0/1,000 in persons who were ≥ 80 years. The overall incidence of 2
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42 222 chronic conditions was slightly higher in women compared to men (overall standardized
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44 223 incidence rates 38.8 vs. 35.5/1,000 person-years; Table 1). The incidence of 2 chronic
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46 224 conditions was higher in Blacks compared to Whites, but lower in Asians compared to
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48 225 Whites (see standardized incidence rates in Table 1 and Figure 2). We observed
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50 226 similar patterns for the development of 3 chronic conditions (see standardized incidence
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52 227 rates in Table 2 and Figure 2). The overall incidence of 3 conditions was similar in men
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3 228 and women (standardized incidence rates 25.5/1,000 person-years in men vs.
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5 229 26.6/1,000 person-years in women); however, it was higher in Blacks and lower in
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8 230 Asians, compared to Whites (Figure 2).
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10 231 In the set of sensitivity analyses in which we combined hyperlipidemia and
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12 232 hypertension as a single condition, we observed a slight decrease in the incidence of 2
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14 233 chronic conditions and of 3 chronic conditions compared with the primary analyses.
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16 234 The overall incidence rate of 2 conditions decreased from 35.0 to 34.0/1,000 person-
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18 235 years in men and from 40.3 to 40.0/1,000 person-years in women. The incidence rate
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20 236 of 3 conditions decreased from 24.7 to 22.5/1,000 person-years in men and from 28.5 to
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22 237 27.0/1,000 person-years in women (incidence rates non-standardized; data not shown
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24 238 in the Tables). For both 2 and 3 conditions, the decrease in incidence was more
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26 239 sizeable in men than in women.
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34 241 **Incidence of dyads and triads**

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37 242 Table 3 shows the incidence of the most common dyads or triads of chronic conditions
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39 243 in seven age strata and for men and women separately. **As expected**, the incidence of
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41 244 dyads and triads varied extensively with age. For example, the most common incident
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43 245 dyad in persons 0-19 years was depression and asthma (1.8/1,000 person-years in
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45 246 boys or men and 2.9/1,000 person-years in girls or women). By comparison, the most
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47 247 common dyad in persons ≥ 80 years was hypertension and cancer in men (18.9/1,000
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49 248 person-years) and hypertension and arthritis in women (27.7/1,000 person-years).
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51 249 Similarly, the most common incident triad of conditions in persons aged 0-19 years was
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53 250 depression, asthma, and substance abuse disorders in both sexes. By comparison, the
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3 251 most common incident triads in persons ≥ 80 years were hypertension, cancer, and
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5 252 arrhythmia in men and hyperlipidemia, hypertension, and arthritis in women.

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8 253 **As expected**, the incidence of dyads and triads also varied by sex. In some
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10 254 instances, the composition of the dyads or triads was the same for men and women, but
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12 255 the magnitude of the incidence rate was different. In other instances, the magnitude of
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14 256 the incidence rate was similar in men and women, but the composition of the dyads and
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16 257 triads varied by sex. For example, the most common incident dyad in persons aged 60-
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18 258 69 years was hyperlipidemia and hypertension in both sexes, but the incidence rate was
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20 259 higher in men compared to women (23.4/1,000 person-years vs. 18.8/1,000 person-
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22 260 years). By contrast, the incidence rates of the most common triads in persons aged 60-
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24 261 69 years were similar in men and women (11.6/1,000 vs. 10.3/1,000 person-years);
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26 262 however, they included different conditions (Table 3).
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33 34 264 **DISCUSSION**

35 36 37 265 **Statement of the principal findings**

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39 266 The burden of multimorbidity in the United States is high and is increasing with an aging
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41 267 population and with improvements in survival. We leveraged a unique longitudinal data
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43 268 resource covering an entire, stable, and geographically defined population to examine
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45 269 the incidence of multimorbidity across all ages. The incidence of 2 chronic conditions
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47 270 and the incidence of 3 chronic conditions increased steeply with older age, and the
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49 271 overall risk was similar in men and women. However, the number of people who
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51 272 developed multimorbidity before age 65 was more than four times greater than the
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53 273 number of people who developed multimorbidity after age 65. The incidence of
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3 274 multimorbidity was highest in Blacks, and lowest in Asians. Finally, **as expected**, the
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5 275 combinations of conditions in incident dyads and triads differed extensively by age and
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8 276 by sex. These results have important implications for identifying individuals at higher
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10 277 risk of developing multimorbidity at different ages. These data are also a first step
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12 278 toward understanding the causes and the consequences of multimorbidity.
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18 280 **Strengths and limitations**

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20 281 A unique strength of our study was the ability to measure the incidence of multimorbidity
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22 282 documented in medical records across seven age groups and for an entire,
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24 283 geographically defined population. We used historical data both to exclude individuals
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26 284 with prevalent multimorbidity at baseline and to follow individuals over a long period of
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28 285 time to accurately document the development of incident multimorbidity. In total, our
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30 286 findings reflect 19 years of data accumulation (5 years before and 14 years after the
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32 287 baseline date).
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37 288 Unfortunately, there is no standard definition of multimorbidity. Previous studies
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39 289 have included a wide range of chronic conditions and a wide range of time frames. We
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41 290 defined multimorbidity using the 20 conditions selected by US-DHHS which were
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43 291 chosen because they “meet the definition for chronicity, are prevalent [common], and
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45 292 are potentially amenable to public health or clinical interventions or both.”²³ However,
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47 293 this definition provides equal weight to each of the 20 conditions without considering the
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49 294 impact of combinations of specific conditions on the quality of life of patients, the
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51 295 complexity of their joint management, and the severity of their long-term outcomes. **In**
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54 296 **addition, this list does not include a number of conditions that may have a**
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3 297 **significant impact on the burden of multimorbidity in older subjects (e.g., hearing**
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5 **and vision problems). Such conditions should be considered in future studies of**
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8 299 **multimorbidity. By contrast, the list includes some conditions that were less**
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10 **common in the general population. For example, autism appeared as part of an**
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12 **incident dyad in only 31 persons, and HIV infection in only 41 persons.**
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15 302 **Therefore, further efforts are needed to refine the list of the most relevant**
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17 **conditions to study multimorbidity, recognizing that the most relevant conditions**
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19 **will vary depending on the age and sex of the population.**
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22 305 Some of the dyads and triads derived by the combination of the 20 conditions
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24 306 selected by the US-DHHS may have a much stronger impact on the complexity of
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26 307 clinical management than others.²⁷ Therefore, some dyads or triads may be
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28 308 particularly costly for the health system, harder for the patient to manage by
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30 309 themselves, less amenable to a single disease approach to care (e.g., telemonitoring for
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32 310 heart failure), and may have a stronger effect on functionality, severity of symptoms,
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34 311 and risk of death. In addition, social factors (e.g., inadequate insurance, low education)
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36 312 and behavioral factors (e.g., poor diet) not reflected in the list of 20 US-DHHS
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38 313 conditions may be as important, or more important, than the 20 conditions in
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40 314 determining the complexity of clinical management and long-term outcomes.²⁷
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46 315 For example, because hyperlipidemia and hypertension are typically
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48 316 asymptomatic, and are often diagnosed as the result of routine screening, their
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50 317 combination is likely to have a much lower impact on the life of the patient than the
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52 318 combination of schizophrenia and heart failure. However, both combinations are
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54 319 considered multimorbidity by the US-DHHS definition. Our sensitivity analyses highlight
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3 320 this problem. As expected, when hyperlipidemia and hypertension were considered as
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6 321 a single condition, the overall incidence of multimorbidity decreased. The decreases
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8 322 were relatively small but were more sizeable in men than in women. These findings
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10 323 emphasize the importance of reaching consensus on the list of conditions to be used to
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12 324 define multimorbidity. However, it is difficult to assess the utility of the 20 conditions
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15 325 included in the US-DHHS list without also understanding how different combinations of
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17 326 these conditions impact long term outcomes. Therefore, we plan to continue this initial
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20 327 incidence study with further analyses to assess which combinations of conditions have
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22 328 the greatest impact on adverse outcomes, including patient quality of life and complexity
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24 329 of clinical management.²⁷

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27 330 We defined incident multimorbidity as the date on which a person met the criteria
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29 331 for a second condition or for a third condition. We used an approach similar to that
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31 332 used in the definition for the onset of metabolic syndrome (reaching three of five
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33 333 components of the syndrome).^{28,29} This simple operational definition of incident
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35 334 multimorbidity should be easy to replicate, and should facilitate future comparisons with
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37 335 other populations.

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40 336 Potential limitations of our study include the inability to validate the ICD-9 codes.
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42 337 It was not possible to confirm all diagnoses for the entire study population, and some
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44 338 ICD-9 codes may have been assigned in error (e.g., “rule out” diagnostic codes). To
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46 339 reduce the likelihood of a single ICD-9 code error, we required two or more diagnosis
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48 340 codes separated by more than 30 days for a person to be defined as having a condition.
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51 341³⁰ However, if a person received a valid code and was lost to follow-up or died rapidly
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53 342 after diagnosis, we may have underestimated the incidence of some of the conditions.
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3 343 In addition, we used diagnosis date as a proxy for the true date of onset of the
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5 344 condition.

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8 345 Some individuals may have moved into Olmsted County after having been
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10 346 diagnosed with one or more chronic conditions elsewhere. If those persons continued
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12 347 to receive care within the REP for a number of years, we captured their chronic
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14 348 condition at the time of subsequent health care visits. However, we did not know the
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16 349 true date of onset for the condition, and the sequence of accumulation of conditions
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18 350 could be distorted. Because the population of Olmsted County is stable, particularly
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20 351 among persons who are 40 years of age or older,¹⁹ we do not expect a major distortion
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22 352 of the multimorbidity incidence rates observed in this study due to migration.
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27 353 Finally, our study focused on a single geographically defined US population, and
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29 354 the incidence of multimorbidity may differ in other populations. However, the
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31 355 demographic and socioeconomic characteristics of our population are similar to those of
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33 356 the upper Midwest of the United States,²⁰ and the prevalence of multimorbidity in
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35 357 persons 65 years of age or older was similar in our population compared with the entire
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37 358 US Medicare population.¹⁶ Replication of this study in other populations in the United
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39 359 States and worldwide will allow for useful comparisons.³¹
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46 361 **Comparison with other studies**

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49 362 A number of studies have described the prevalence of multimorbidity in various
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51 363 populations;^{1,7-12} however, few studies have described the incidence of multimorbidity,
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53 364 and no incidence studies are available for the US. In 1998, Van den Akker and
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55 365 colleagues estimated the one year incidence of multimorbidity in patients from a
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3 366 network of family practices in the Netherlands.³² Incident multimorbidity was defined as
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5 367 the new development of at least 2 of 335 diagnostic categories within a one year period.
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8 368 Overall, 7.9% of their population developed one new disease and 1.3% developed two
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10 369 or more new diseases in one year. The proportion of people who developed two or
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12 370 more new conditions increased with older age, but did not differ substantially by sex. It
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14 371 is difficult to compare our results directly to the Dutch findings because of
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16 372 methodological differences (e.g., number of conditions considered and time frame), and
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18 373 because it is not clear whether some of the participants in the Dutch study already had
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20 374 one or more conditions at baseline. However, we observed similar patterns of
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22 375 increasing incidence with older age, and limited differences between men and women in
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24 376 overall incidence.
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29 377 More recently, Melis and colleagues assessed the incidence of multimorbidity in
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31 378 Swedish people aged 75 years or older at baseline who participated in a longitudinal
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33 379 cohort study.³³ Incident multimorbidity was defined as the development of at least 2 of
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35 380 39 chronic conditions during three years of follow-up. Participants with none of the 39
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37 381 chronic conditions at baseline had a multimorbidity incidence rate of 12.6 per 100
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39 382 person-years, and patients with one of the 39 conditions at baseline had an incidence
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41 383 rate of 32.9 per 100 person-years. Although we examined fewer conditions than the
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43 384 Swedish group (20 vs. 39), and the ascertainment of incident conditions was different
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45 385 (medical records data vs. survey methods), our incidence rates of multimorbidity in
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47 386 subjects aged 75 years or older were similar (19.1 per 100 person-years in people with
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49 387 no conditions at baseline and 38.9 per 100 person-years in persons with one condition
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51 388 at baseline; both sexes combined; data not shown).
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390 **Meaning of the study**

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

405 Prior studies of the prevalence of multimorbidity have shown a dramatic increase
406 in the number of people living with 2 or more chronic conditions at older ages.^{1,7-11}
407 However, the high prevalence of multimorbidity in the older population implies that
408 relatively few older individuals remain at risk of developing multimorbidity. Overall,
409 among persons aged 80 years or older at baseline, only 891 out of 3,710 (24.0%) were
410 at risk of developing 2 chronic conditions (the other 76.0% already had 2 or more of the
411 20 conditions). Although the persons who reached 80 years of age or older and

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3 412 **remained free of multimorbidity were a particularly resilient group, they had a**
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5 413 **higher risk of developing subsequent multimorbidity than younger persons.**
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8 414 We also found that the total number of people who developed multimorbidity
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10 415 before age 65 years was more than 4 times greater than the number of people who
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12 416 developed multimorbidity at ages 65 or older (28,378 vs. 6,214). These data emphasize
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14 417 the need to target preventive efforts at much younger ages, but represent only a first
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16 418 step toward future research to identify the social, behavioral, and clinical risk and
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18 419 protective factors for multimorbidity.
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22 420 We found important differences in the incidence of multimorbidity by ethnicity.
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24 421 The age standardized incidence rates of multimorbidity were higher in Blacks and lower
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26 422 in Asians compared to Whites. Our findings are consistent with previous studies that
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28 423 showed a higher prevalence of multimorbidity in Blacks compared to Whites, but a lower
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30 424 prevalence of multimorbidity in Asians.^{8,16,36-38} Our data suggest that some of these
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32 425 differences in prevalence may be attributed to differences in the incidence of the
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34 426 conditions among different ethnic groups. However, differential survival may also
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36 427 contribute to the differences in prevalence. In turn, both differences in incidence and in
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38 428 prevalence may be influenced by socioeconomic factors, lifestyle behaviors, social
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40 429 environment, and healthcare access. Further research is needed to better characterize
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42 430 these disparities and to identify the causal mechanisms that contribute to different
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44 431 development of chronic conditions and to different survival.
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50 432 **As expected**, the incidence and the composition of the dyads and triads of
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52 433 conditions varied extensively across age and sex strata. For example, women 20 years
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54 434 of age or older were more likely to have depression as a component of their incident
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3 435 multimorbidity dyads and triads compared to men. Such differences may lead to
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6 436 different long-term outcomes in men and women. Therefore, these data are useful to
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8 437 understand how multimorbidity develops, and are an important first step toward future
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10 438 research. In particular, such incident data are necessary to study the chronological
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12 439 order of acquisition of multiple chronic conditions in different age, sex, and ethnic strata.
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15 440 Incidence data are also necessary to determine whether the differential order of
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17 441 acquisition is associated with a different risk of adverse long-term outcomes such as
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19 442 hospitalizations, emergency department visits, or death. For example, it is not clear
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21 443 whether acquiring depression prior to arthritis results in worse long-term outcomes
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23 444 compared with acquiring arthritis prior to depression. Future studies are also needed to
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25 445 understand how additional chronic conditions accumulate after the development of a
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27 446 second and third condition. **Finally, the incidence of specific dyads and triads**
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29 **reflects the incidence of the individual conditions in specific age and sex groups.**
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31 **Many of these dyads and triads are expected to develop simply by chance.**
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33 **Therefore, future studies are needed to identify the dyads and triads that co-**
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35 **occur beyond chance. Identification of incident dyads and triads that reflect**
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37 **shared etiologic mechanisms or shared risk factors may lead to combined**
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39 **treatment or prevention strategies.**
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50 **Conclusions and clinical implications**

51 455 It is important and urgent to understand the causes and the consequences of
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53 456 multimorbidity to inform efforts to delay and prevent disease onset and to develop
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55 457 effective strategies for caring for patients with multimorbidity. We studied the incidence
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3 458 of multimorbidity across all ages, separately in men and women, and in three ethnic
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6 459 groups in a geographically defined US population. The incidence of multimorbidity
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8 460 increased steeply with older age and was higher in Blacks but lower in Asians
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10 461 compared to Whites. Men and women had a similar overall risk, but the combinations
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12 462 of conditions within dyads and triads varied extensively by age and by sex. These data
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14 463 represent an important first step toward **identifying conditions which co-occur more**
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16 **frequently than chance alone, identifying** specific risk factors for multimorbidity,
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18 understanding how chronic conditions accumulate over time, and toward identifying
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20 **combinations of conditions that predict** adverse outcomes.
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3 467 **Competing interest declaration:**
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5
6 468 All authors have completed the Unified Competing Interest form at
7
8
9 469 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author)
10
11 470 and declare that (1) none of the authors have support from any companies for the
12
13 471 submitted work; (2) none of the authors have any relationships with any companies that
14
15 472 might have an interest in the submitted work in the previous 3 years; (3) their spouses,
16
17 473 partners, or children have no financial relationships that may be relevant to the
18
19 474 submitted work; and (4) none of the authors have any non-financial interests that may
20
21 475 be relevant to the submitted work.
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26 476 **Contributorship statement:** Dr. St. Sauver had full access to all of the data in the
27
28 477 study and takes responsibility for the integrity of the data and the accuracy of the data
29
30 478 analysis. She is the guarantor for the study.
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32
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34 479 *Study concept and design:* St. Sauver, Boyd, Grossardt, Yawn, Rocca.
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37 480 *Acquisition, analysis, or interpretation of data:* St. Sauver, Grossardt, Rocca.
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40 481 *Drafting of the manuscript:* St. Sauver, Rocca.
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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.

Ethnicity age (years)	Men			Women		
	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

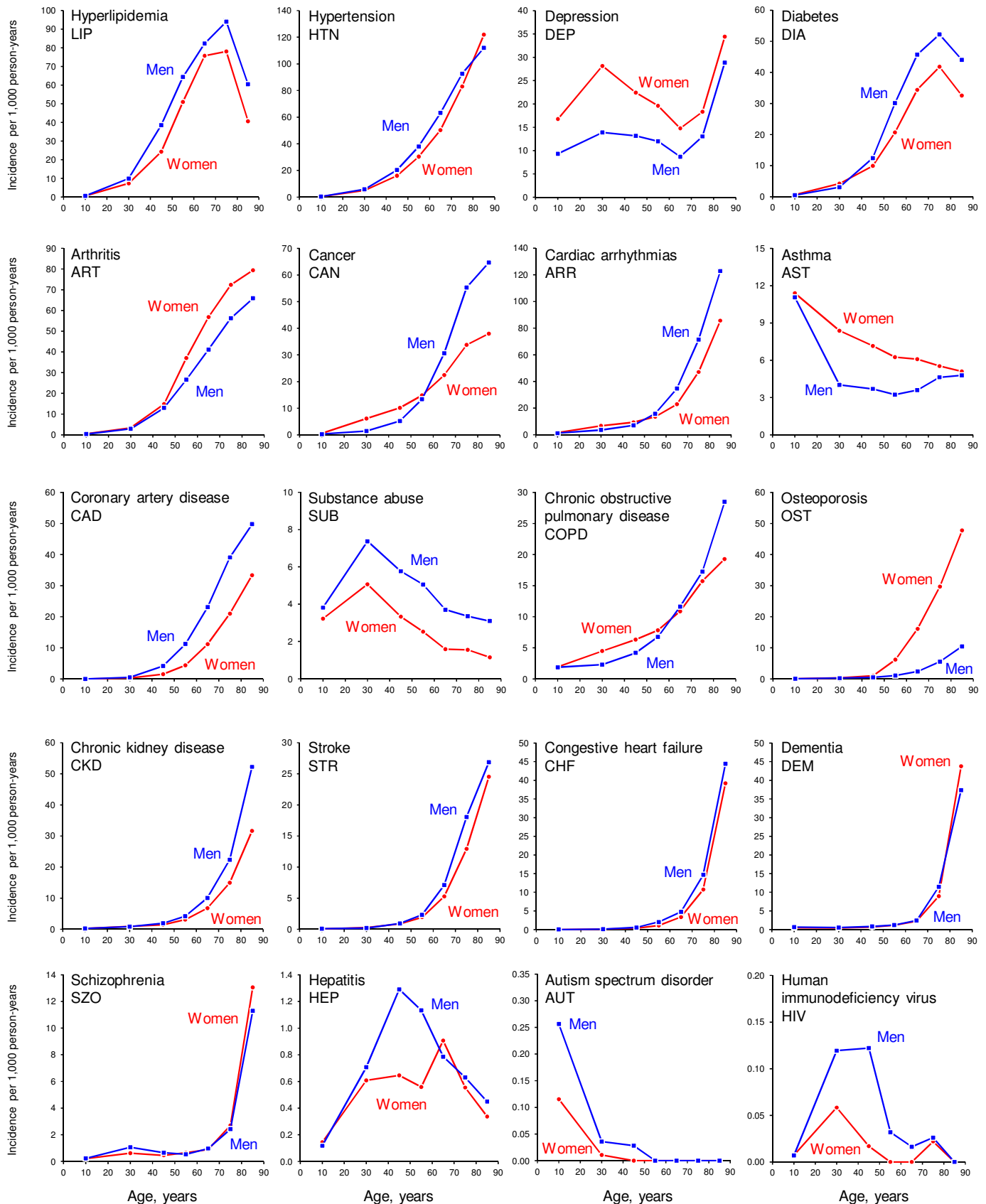
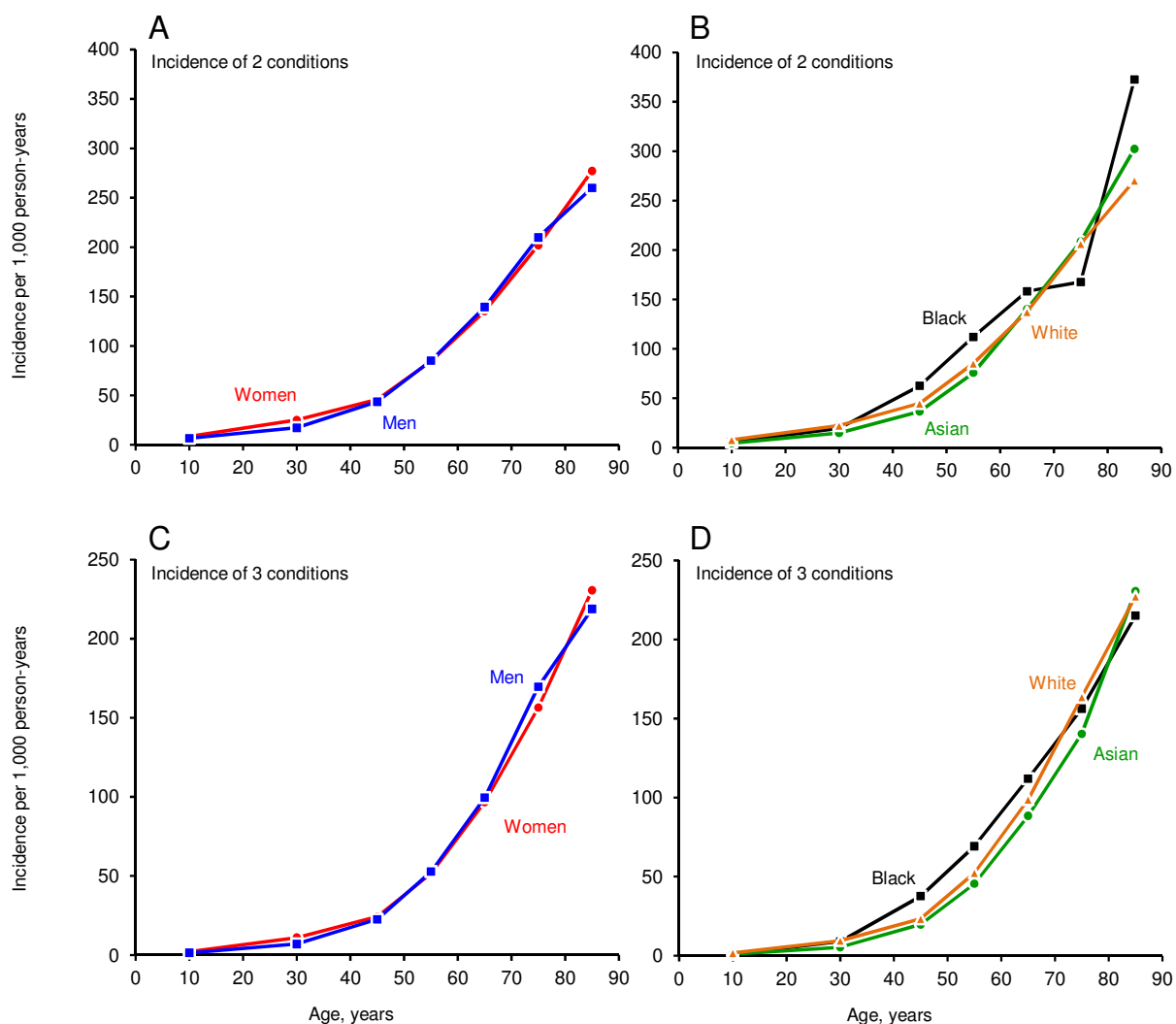


Figure 2



view only

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			Women		
	Persons	Person- years	Incidence rate * (n)	Persons	Person- years	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)

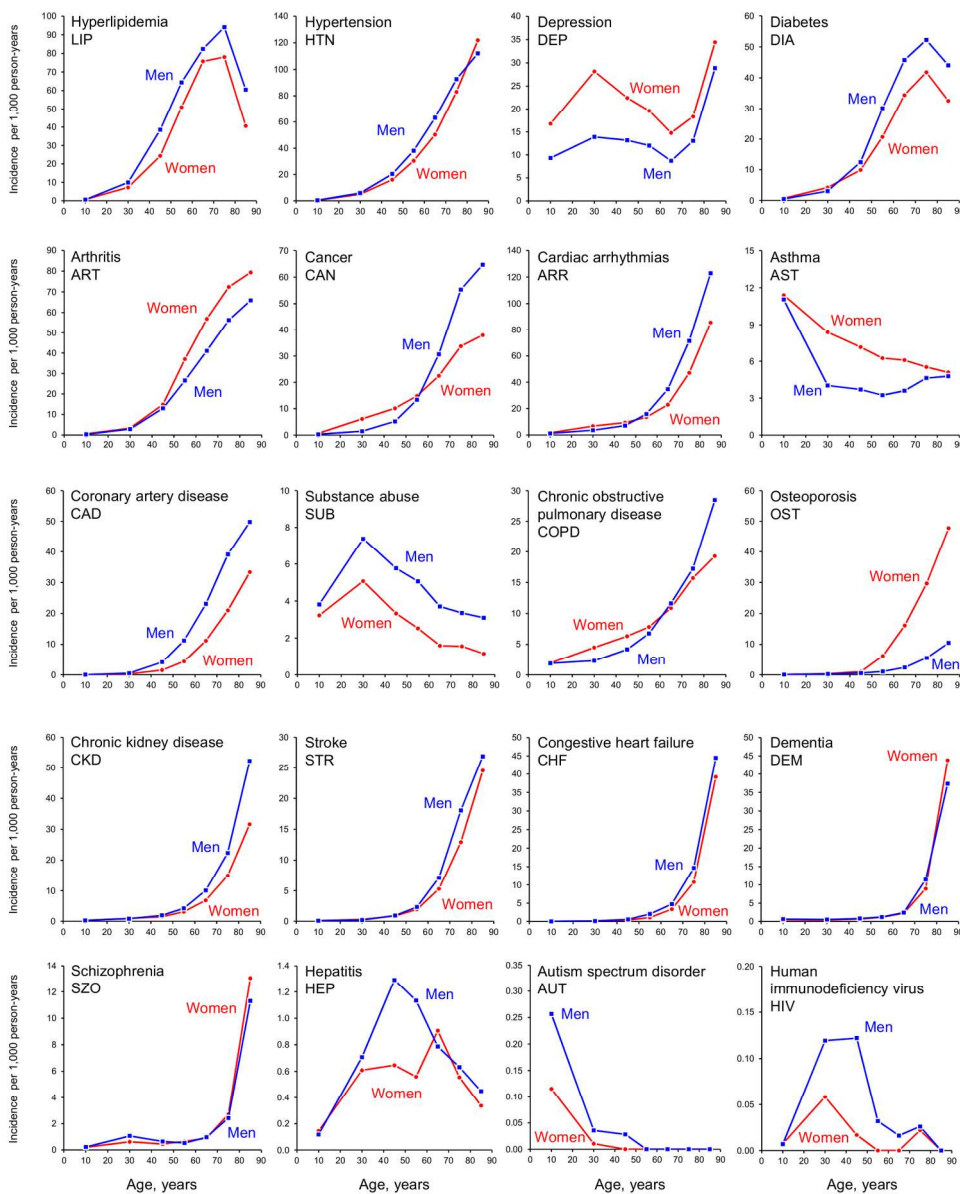


Figure 1. Age- and sex-specific incidence rates (per 1,000 person-years) of the 20 chronic conditions considered separately. The 20 panels are presented by rows in decreasing order of frequency (by overall age- and sex-standardized prevalence). 16 173x215mm (300 x 300 DPI)

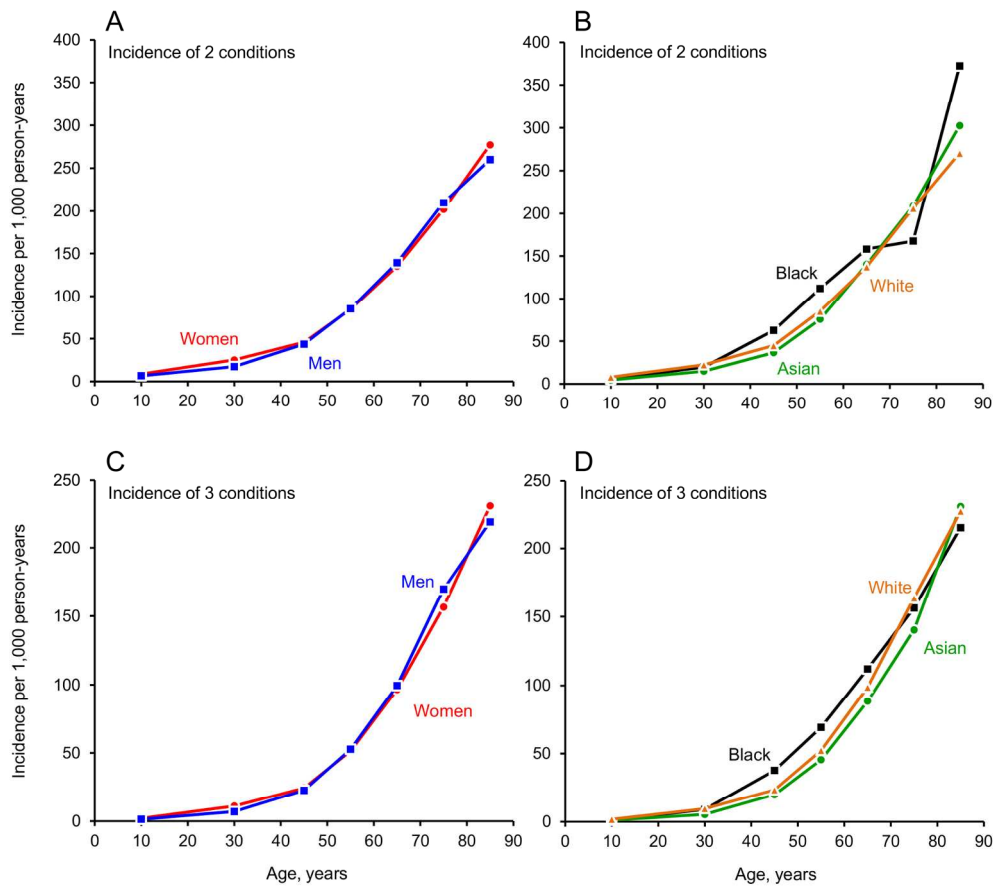


Figure 2. Incidence rates (per 1,000 person-years) of 2 chronic conditions (second condition in a dyad) and of 3 chronic conditions (third condition in a triad) in men and women separately (panels A and C), and stratified by ethnicity (panels B and D).
173x154mm (300 x 300 DPI)

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			Women		
	Persons	Person- years	Incidence rate * (n)	Persons	Person- years	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.