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BRIEF REPORT

Lupus, a Leading Cause of Years of Potential Life Lost in Young Women: Implications for Public Health Priorities and Research Funding

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Objective. Premature mortality burden is an important component of disease burden and can help guide health care and research priorities. However, relying solely on mortality rates may underestimate lupus mortality burden because a substantial proportion of deaths occur at younger ages. Years of potential life lost (YPLL) captures premature mortality by applying a predefined age threshold. We estimated the YPLL from lupus in US women relative to leading causes of death and other autoimmune diseases.

Methods. Using the US population–based national Multiple Cause-of-Death database, we obtained death counts for 28 diseases, including lupus, the Centers for Disease Control and Prevention's 15 leading causes of death, and 12 additional autoimmune diseases. We calculated YPLL before age 75 years by summing 75 minus age at death for deaths occurring before age 75. Official cause-of-death rankings were obtained from the Web-based Injury Statistics Query and Reporting System (WISQARS). Sensitivity analyses were repeated in female decedents during 2018 to 2024.

Results. From 2000 to 2015, 304.2 thousand years were lost to lupus in US women aged 15 to 44 years. Lupus-associated YPLL ranked 14th in women aged 15 to 44 years and 9th in women aged 15 to 24, exceeding diabetes mellitus, HIV disease, septicemia, chronic lower respiratory disease, anemias, nephritis, and cerebrovascular disease. Among autoimmune diseases, lupus YPLL ranked first in women aged 15 to 24 years and second in women aged 15 to 44 years.

Conclusion. Lupus is a major contributor to premature mortality in young women. Quantifying premature mortality burden through YPLL provides a complementary public health perspective and may inform prioritization of research and public health initiatives.

INTRODUCTION

Disease burden encompasses the impact of a health condition on a specific region or population, serving as a vital tool for establishing health care and research priorities while pinpointing high-risk groups. It can be gauged through various metrics, including morbidity, disability, financial cost, and mortality. We previously reported that lupus mortality remains disproportionately high compared to mortality rates in the general population.[1,2] However, in the commonly reported crude and age-adjusted mortality, the weighted emphasis is placed on natural causes of death in the elderly. Therefore, relying solely on mortality rates may not provide a comprehensive mortality burden of lupus,[3] as a substantial proportion of those who succumb to the disease do so before the age of 45.[1,4] Premature mortality, therefore, represents a crucial measure for quantifying disease burden.[5]

The years of potential life lost (YPLL) represents mortality as years of healthy life lost due to premature death.[6] It takes into account the age at which deaths occur, giving greater weight to deaths at a younger age and lower weight to deaths at older age. YPLL is used in public health planning to compare the relative importance of different causes of premature death within a given population, to set priorities for prevention, and to compare

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the premature mortality experience between populations. For diseases such as lupus, which frequently affect young women and may lead to death during adolescence, early adulthood, or midlife, YPLL may provide a more informative measure of mortality burden than mortality rates alone. To our knowledge, there are no reports of large population-level YPLL in lupus.

Lupus is a predominantly female, chronic autoimmune disease. Of 62,843 lupus deaths in the US national mortality database, 84% were in women.[1] Furthermore, placement of lupus deaths among Centers for Disease Control and Prevention (CDC)'s leading causes-of-death ranking list revealed that lupus ranked within the top 15 leading causes of death in reproductive age (15–44 years) women, including its 10th ranking in the 15- to 24-year-old female decedents.[7] After excluding the three common external injury causes of death (unintentional injury, suicide, and homicide) from analysis, lupus ranked 5th among Black and Hispanic women and 7th among all women in the 15- to 24-year age group. These findings underscore lupus as an important public health issue in young women and suggest that premature mortality is a key component of lupus burden.

To assess the relative burden of lupus among the leading causes of premature death in young women, we measured YPLL in reproductive age (15–44 years) female decedents for lupus relative to the CDC's top 15 leading causes of death. Since lupus is among the top 10 leading causes of death in 15- to 24-year-old female decedents, we repeated YPLL measurements in this age group. To determine the burden of premature lupus mortality relative to other autoimmune diseases, which are also common in young women, we measured YPLL for 12 other autoimmune diseases. We also describe National Institutes of Health (NIH) funding for lupus relative to several diseases with similar premature mortality burden. This study adds to previous mortality work by using YPLL to provide a complementary public health perspective on lupus mortality in young women.

MATERIALS AND METHODS

Data source. This is a population-based study using CDC's National Vital Statistics System mortality database,[8] which maintains data provided by various jurisdictions that are legally responsible for the registration of vital events and information extracted from death certificates. This database encompasses more than 99% of deaths of US residents in all 50 states and the District of Columbia.

Data on death counts were obtained from the CDC's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause-of-Death database for 16 years (2000–2015), as described previously.[7] The multiple-cause-of-death file includes both the underlying cause of death and contributing causes recorded on each death certificate. Number of deaths in women were tabulated for 28 diseases, including the top 15 leading causes of death from CDC's official leading-causes-of-death ranking,[7] lupus, and 12 other autoimmune diseases at different ages using the *International Classification of Diseases* (ICD)–10 codes. ICD-10 codes for all diseases in this study are included in the respective figures and tables. Data on the leading causes of death were also obtained from the CDC WONDER Web-based Injury Statistics Query and Reporting System (WISQARS) database, the CDC's web-based injury statistics and reporting system.[7] For autoimmune diseases, deaths were identified when the disease was listed as either an underlying cause or a contributing cause of death. Because multiple causes can be listed on a single death certificate, disease-specific counts in the multiple-cause-of-death data set are not mutually exclusive. Accordingly, a single death record could contribute to more than one disease-specific count if more than one qualifying conditions were listed.

Data on funding for lupus and other diseases were retrieved from the NIH Research Portfolio Online Reporting Tools (RePORT), the NIH public reporting system for categorical research spending. The funding analysis was limited to publicly reported NIH categorical spending and does not include support from other federal agencies, foundations, or industries.

YPLL calculation. We calculated YPLL before age 75 years for each condition as: $\Sigma(d_i \times [75 - age_i])$ for deaths occurring at ages <75 years, where d_i is the number of deaths at age i. We selected age 75 years because it is close to US life expectancy, and YPLL before age 75 is a widely used public health threshold in the United States.

Sensitivity analysis. We repeated the aforementioned analyses, including YPLL calculation and ranking, in female US decedents from 2018 to 2024 as a sensitivity analysis.[9]

RESULTS

There were 28,411 deaths with lupus recorded as the underlying or a contributing cause of death in women from 2000 through 2015. In the sensitivity analysis (2018–2024), 24,531 female decedents had lupus recorded as a cause of death. The age distribution of female lupus deaths and the ranking of lupus deaths relative to the CDC's official 20 leading causes of death in women[7] revealed that lupus ranked among the top 15 leading causes of death at ages 15 to 24, 25 to 34, and 35 to 44 during both time periods (2000–2015 and 2018–2024) (Supplemental Table S1). The highest ranking of lupus among the leading causes of death was seen at 15 to 24 years of age in both time periods.

The YPLL for lupus relative to the official 15 leading causes of death in women is shown in Figure 1. From 2000 to 2015, 304.2 thousand years were lost to lupus in reproductive age (15–44 years) female decedents where lupus ranked as the 14th leading cause of death. Lupus ranked higher (9th) in the 15- to 24-year age group, above diabetes mellitus, HIV, septicemia, chronic

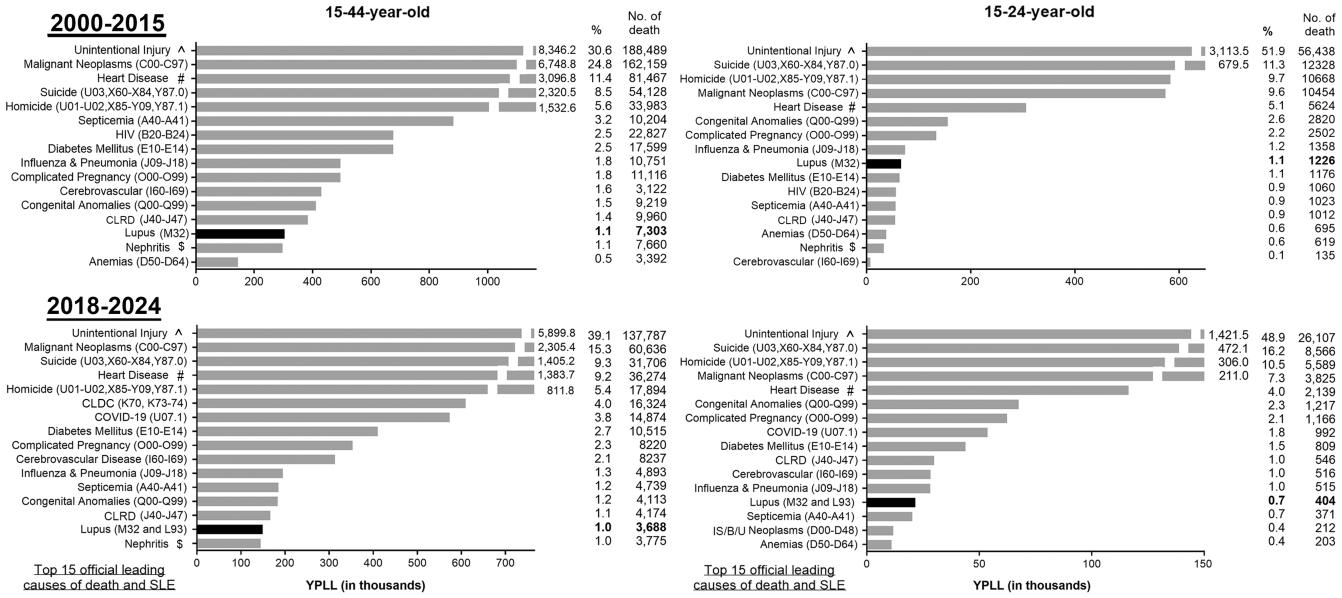

Figure 1. YPLL for lupus relative to the official 15 leading causes of death in the United States, 2000 to 2015 (upper panels), and 2018 to 2024 (lower panels). YPLL before age 75 years among female deaths at 15- to 44-years of (reproductive) age (left panels) and 15- to 24-years of age (right panels) was estimated for the Centers for Disease Control and Prevention's top 15 leading causes of death and for lupus. Numbers on the bars represent the proportion of YPLL for the listed causes of death. ICD-10 codes: ^V01-X59, Y85-Y86; #I00-I09, I11, I13, I20-I51; $N00-N07, N17-N19, N25-N27. CLDC, chronic liver disease and cirrhosis; CLRD, chronic lower respiratory disease; ICD, *International Classification of Diseases*; IS/B/U, in situ, benign, and unknown; SLE, systemic lupus erythematosus; YPLL, years of potential life lost.

lower respiratory disease, anemias, nephritis, and cerebrovascular disease (Figure 1, 2000–2015). After excluding the three common external injury causes of death (unintentional injury, suicide, and homicide) from analysis, lupus ranked 11th in the 15- to 44-year age group and 6th in the 15- to 24-year age group. In sensitivity analyses (Figure 1, 2018–2024), lupus YPLL ranked 13th in the 15- to 24-year age group and 15th in all reproductive age women. Despite the high YPLL ranking, NIH research funding for lupus is lower relative to several other leading causes of death (Table 1).

Finally, we measured YPLL for lupus relative to 12 other common autoimmune diseases (Figure 2). Lupus ranked number

Table 1. NIH categorical research funding for the leading causes of death and lupus*

Leading causes[a]	2013[b]	2023[b]	2024[b]
Accidents (unintentional injuries) (V01–X59, Y85–Y86)	367	894	892
Malignant neoplasms (C00–C97)	5,274	7,968	8,050
Diseases of heart (I00–I09, I11, I13, I20–I51)	1,230	1,883	1,769
Intentional self-harm (suicide) (U03, X60–X84, Y87.0)	37	187	190
Assault (homicide) (U01-U02, X85–Y09, Y87.1)	<0.5	8	12
Chronic liver disease and cirrhosis (K70, K73–K74)	282	447	444
COVID-19 (U07.1)	NA	132	106
Diabetes mellitus (E10–E14)	1,007	1,187	1,151
Cerebrovascular diseases (I60–I69)	282[c]	1,140	1,164
Pregnancy, childbirth and the puerperium (O00–O99)	215[d]	702	644
Influenza and pneumonia (J09–J18)	407	654	619
Septicemia (A40–A41)	88	191	182
Chronic lower respiratory diseases (J40–J47)	333	469	461
Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	NA	636	596
Lupus (M32, L93)	92	138	138
Nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27)	551	703	717

**Source*: NIH RePORT categorical spending data. NA, funding support data not available before the initial year reported; NIH, National Institutes of Health; RePORT, Research Portfolio Online Reporting Tools.
[a]In 15- to 44-year-old female decedents.
[b]Dollars in millions and rounded.
[c]Stroke.
[d]Preterm, low-birth weight, and health of the newborn; teenage pregnancy.

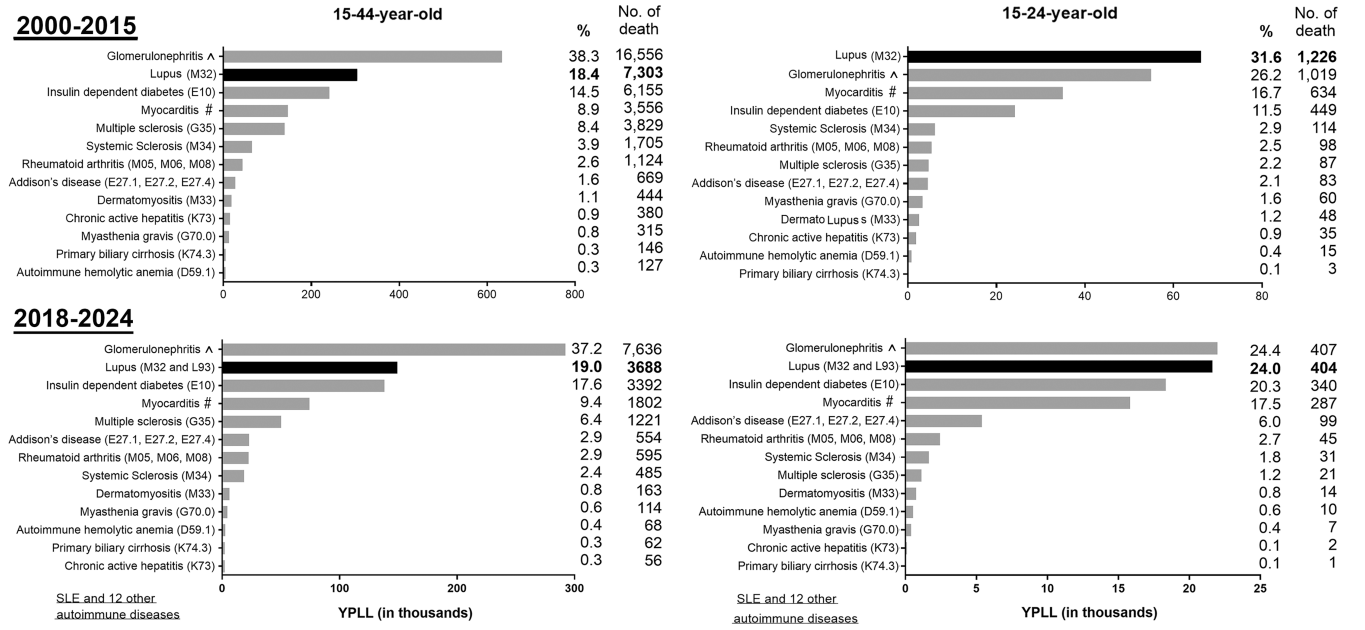

Figure 2. YPLL in women for lupus relative to other autoimmune diseases in the United States, 2000 to 2015 (upper panels) and 2018 to 2024 (lower panels). YPLL before age 75 years among women deceased at 15 to 44 years (reproductive age) (left panels) and 15 to 24 years of age (right panels) was estimated for selected autoimmune diseases. Numbers on the bars represent the proportion of YPLL for the listed causes of death. ICD-10 codes: ^N00, N01, N03, N05, N18; #I40.1, I40.8, I40.9, I51.4, I51.8. ICD, *International Classification of Diseases*; SLE, systemic lupus erythematosus; YPLL, years of potential life lost.

1 in the 15- to 24-year age group and number 2 in all reproductive age women (2000–2015) and number 2 in both age groups (2018–2024).

DISCUSSION

This study is the first population-based estimation of lupus-associated YPLL. It applies YPLL to provide a complementary public health measure of premature lupus mortality burden relative to both the leading causes of death and other autoimmune diseases in young women. We highlight that lupus is among the leading causes of YPLL in young women and a top cause of YPLL among common autoimmune diseases in young women.

YPLL is used as a measure to highlight the specific causes of deaths within younger age groups.[6] In constructing YPLL as a measure of premature death, an arbitrary limit to life is chosen, thus causing any death later than that age to contribute nothing to the burden of disease.[3] This methodologic issue is particularly influential if a large number of patients with a disease live past the cutoff age with good quality of life. For example, in the only report that we found of YPLL in lupus, 50 decedents from Oslo, Norway, 1999 to 2009, had YPLL calculated before 60 years of age,[4] which will affect estimates of premature death burden because a substantial proportion (36%–51%) of lupus deaths occur after 65 years of age (Supplemental Table S1). Hence, we used 75 years as the predefined upper age limit for calculating YPLL.

A larger YPLL can be attributed to a greater number of deaths, younger ages at death, or a combination of both. It is encouraging that the proportion of deaths in the <45-year age group decreased from 26.1% during 2000 to 2015 to 15.1% during 2018 to 2024, with a lower ranking of lupus YPLL in 2018 to 2024 than in 2000 to 2015.

Use of the largest female lupus decedent population to date (52,942) and an unbiased inclusion of all US deaths are strengths of this study. However, the results of studies using national mortality databases should be interpreted with some caution.[8] A limitation is the quality of information given on the death certificates. Underrecording of lupus on death certificates likely biases estimates downward because lupus may not be recorded on the death certificates in as many as 32% to 59% of patients with lupus in the United States.[8] Furthermore, the ranking for some other leading causes of YPLL may be higher than their actual rank; for example, death certificates tend to overestimate cardiovascular disease mortality.[10] The likelihood of overestimating lupus mortality is low, because lupus is unlikely to be perceived as a proximate cause of death without clear clinical manifestations. Consistently, only 2 (0.27%) of the 731 decedents for whom lupus was recorded on the death certificate had lupus erroneously recorded as a cause of death (when the decedents did not have lupus).[11] In addition, because the multiple-cause-of-death data are not mutually exclusive, these rankings should be interpreted as comparisons of disease-specific premature mortality burden rather than a partitioning of all deaths.

Underreporting of lupus on death certificate may occur when deaths are coded under proximate manifestations or complications such as infection, renal failure, nephritis, or cardiovascular disease rather than lupus itself. Death certificate data can also be ambiguous when lupus activity, treatment complications, and related conditions all contribute to a patient's death. Underreporting of lupus on death certificate is less common in younger individuals and those who die of active disease and lupus nephritis but is significantly higher in older lupus decedents and those where the proximate cause of death is deemed to be a cancer or a cardiovascular event.[8,11,12] Thus, while underrecording may affect mortality rates and lower the rank of lupus on the leading-cause list, it is likely to have a relatively smaller impact on YPLL than that on the overall mortality rate. Nevertheless, the lupus-associated YPLL ranked among the top 15 leading causes of death in young women.

YPLL represents the impact of only fatal outcomes on population health. It does not account for the impact of nonfatal health outcomes, which can be measured by the years of life lost due to disability (YLD). In this regard, the disability-adjusted life years represents a measure of overall disease burden and is calculated as the sum of the YPLL (mortality as years of healthy life lost due to premature death) and the YLD (years of healthy life lost due to nonfatal health outcomes).[13] Allocation of public health resources should be based, where feasible, on objective assessments of health status, burden of disease, disability, preventability, and related costs.[3]

In 2023, the NIH's funding for lupus was $138 million in research. This is in comparison to $703 million for nephritis and nephrotic syndrome, $447 million for chronic liver diseases, $1,140 million for cerebrovascular diseases, $1,187 million for diabetes mellitus, and $7,968 million for malignant neoplasms. However, NIH RePORT does not include all other potential sources of support, and NIH funding categories do not map perfectly onto disease categories used in mortality analyses. Therefore, these funding comparisons should be interpreted as contextual rather than definitive.

In conclusion, our findings underscore lupus as an important public health issue in young women. The YPLL ranking gives a new and meaningful perspective regarding premature mortality in lupus and supplements other methods of assessing disease burden. Recognition of lupus as a leading contributor to premature mortality may inform public health reporting, prevention priorities, and research prioritization, while acknowledging that funding decisions across diseases should incorporate multiple dimensions of burden, preventability, and opportunity for impact.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Singh confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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