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Population-Based Study, 2000-2015

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BRIEF REPORT

Lupus—An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000–2015

Eric Y. Yen and Ram R. Singh

Objective. Mortality statistics from the Centers for Disease Control and Prevention (CDC) are used for planning health care policy and allocating resources. The CDC uses these data to compile its annual ranking of leading causes of death based on a selected list of 113 causes. Systemic lupus erythematosus (SLE) is not included on this list. Since the ranking is a useful tool for assessing the relative burden of cause-specific mortality, this study was undertaken to rank SLE deaths among the CDC's leading causes of death to see whether SLE is a significant cause of death among females.

Methods. Death counts for the female population of the US were obtained from the CDC's Wide-ranging Online Data for Epidemiologic Research database and then grouped by age and race/ethnicity. Data on the leading causes of death were obtained from the Web-based Injury Statistics Query and Reporting System database.

Results. During 2000–2015, there were 28,411 deaths of females with SLE recorded as an underlying or contributing cause of death. SLE ranked among the top 20 leading causes of death in females between 5 and 64 years of age. SLE ranked tenth among those ages 15–24 years, fourteenth among those ages 25–34 years and 35–44 years, and fifteenth among those ages 10–14 years. For African American and Hispanic females, SLE ranked fifth among those ages 15–24 years, sixth among those ages 25–34 years, and eighth or ninth among those ages 35–44 years, after the 3 common external injury causes of death were excluded from the analysis.

Conclusion. SLE is among the leading causes of death in young females, underscoring its impact as an important public health issue.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that predominantly affects females and can involve virtually any organ. We recently analyzed secular trends and population characteristics associated with SLE mortality using the US nationwide mortality database comprising 62,843 deaths from SLE, of which 84% were in females (1). We found that although SLE mortality rates have decreased over the past 5 decades, they remain high relative to the mortality rate for all causes other than SLE (non-SLE). In fact, the ratio of the SLE mortality rate to the non-SLE mortality rate was 34.6% higher in 2013 than in 1968. Thus, SLE mortality remains high in the US population.

The National Vital Statistics System of the Centers for Disease Control and Prevention (CDC) maintains a mortality database, with 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 the deaths of US residents in all 50 states and the District of Columbia. Mortality statistics data from this database serve as important indicators of the health of the US population and are used to estimate the burden of specific diseases. Mortality statistics are also used for health care policy planning and resource allocation.

Using the National Vital Statistics System mortality database, the CDC compiles an annual leading causes of death ranking based on a selected list of 113 causes (2). SLE is not included on this list. The cause of death ranking is a useful tool for assessing the relative burden of cause-specific mortality. Hence, we ranked SLE deaths among the CDC's leading causes of death to determine the relative burden of SLE deaths in females.

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Table 1. Twenty leading causes of death of females in the US from 2000 to 2015*

Rank	Ages 5–9 years	Ages 10–14 years	Ages 15–24 years	Ages 25–34 years	Ages 35–44 years	Ages 45–54 years	Ages 55–64 years	Age ≥65 years
1	Unintentional injury (6,052)†	Unintentional injury (6,438)†	Unintentional injury (56,747)†	Unintentional injury (57,741)†	Malignant neoplasms (121,604)	Malignant neoplasms (387,239)	Malignant neoplasms (747,302)	Heart disease (4,468,532)
2	Malignant neoplasms (3,415)	Malignant neoplasms (3,450)	Suicide (12,328)†	Malignant neoplasms (30,101)	Unintentional injury (75,614)†	Heart disease (166,833)	Heart disease (334,259)	Malignant neoplasms (3,046,099)
3	Congenital anomalies (1,420)	Suicide (1,390)†	Homicide (10,746)†	Suicide (17,021)†	Heart disease (57,325)	Unintentional injury (91,853)†	Chronic lower respiratory disease (104,733)	Cerebrovascular disease (978,817)
4	Homicide (948)†	Congenital anomalies (1,302)	Malignant neoplasms (10,454)	Heart disease (16,951)	Suicide (24,778)†	Cerebrovascular disease (42,810)	Diabetes mellitus (75,872)	Chronic lower respiratory disease (1,224,648)
5	Heart disease (726)	Homicide (1,033)†	Heart disease (5,534)	Homicide (12,047)†	Cerebrovascular disease (15,801)	Liver disease (38,999)	Cerebrovascular disease (73,651)	Alzheimer's disease (844,609)
6	Influenza and pneumonia (408)	Heart disease (951)	Congenital anomalies (2,820)	HIV (6,543)	HIV (15,224)	Diabetes mellitus (35,350)	Unintentional injury (63,404)†	Diabetes mellitus (454,459)
7	Chronic lower respiratory disease (337)	Chronic lower respiratory disease (451)	Complicated pregnancy (2,502)	Complicated pregnancy (5,193)	Liver disease (14,919)	Chronic lower respiratory disease (33,297)	Liver disease (41,614)	Influenza and pneumonia (448,129)
8	Benign neoplasms (333)	Influenza and pneumonia (420)	Influenza and pneumonia (1,358)	Diabetes mellitus (4,329)	Diabetes mellitus (12,094)	Suicide (30,842)†	Septicemia (32,722)	Unintentional injury (317,971)†
9	Cerebrovascular disease (299)	Cerebrovascular disease (339)	Cerebrovascular disease (1,357)	Cerebrovascular disease (4,097)	Homicide (11,450)†	Septicemia (17,072)	Nephritis (31,003)	Nephritis (314,704)
10	Septicemia (250)	Benign neoplasms (297)	SLE (1,226)/diabetes mellitus (1,176)	Congenital anomalies (2,897)	Chronic lower respiratory disease (6,948)	Influenza and pneumonia (14,323)	Influenza and pneumonia (24,855)	Septicemia (243,733)
11	Anemias (136)	Septicemia (260)	HIV (1,060)	Influenza and pneumonia (2,888)	Septicemia (6,671)	HIV (13,935)	Suicide (20,156)†	Hypertension (216,273)
12	Perinatal period (122)	Diabetes mellitus (180)	Septicemia (1,023)	Liver disease (2,674)	Influenza and pneumonia (6,505)	Nephritis (13,665)	Hypertension (15,010)	Parkinson's disease (136,101)
13	Meningitis (66)	Anemias (158)	Chronic lower respiratory disease (1,012)	Septicemia (2,510)	Nephritis (5,109)	Viral hepatitis (10,129)	Viral hepatitis (11,449)	Pneumonitis (122,080)
14	Nephritis (66)	Perinatal period (98)	Anemias (695)	SLE (2,431)/chronic lower respiratory disease (2,000)	SLE (3,646)/congenital anomalies (3,502)	Homicide (8,462)†	Benign neoplasms (9,587)	Benign neoplasms (93,021)
15	Diabetes mellitus (56)	SLE (78)/HIV (77)	Nephritis (619)	Nephritis (1,932)	Complicated pregnancy (3,421)	Hypertension (7,302)	Alzheimer's disease (6,283)	Atherosclerosis (89,423)
16	Pneumonitis (33)	Meningitis (74)	Benign neoplasms (614)	Anemias (1,149)	Viral hepatitis (2,499)	SLE (5,271)/benign neoplasms (5,156)	Pneumonitis (5,867)	Liver disease (76,262)
17	Diseases of the appendix (32)	Nephritis (72)	Pneumonitis (250)	Benign neoplasms (1,100)	Benign neoplasms (2,343)	Congenital anomalies (5,134)	Congenital anomalies (5,860)	Aortic aneurysm (69,881)
18	Meningococcal infection (30)	Pneumonitis (41)	Liver disease (188)	Hypertension (673)	Hypertension (2,314)	Pneumonitis (2,923)	HIV (5,804)	Anemias (36,608)
19	HIV (29)	Meningococcal infection (35)	Meningitis (186)	Pneumonitis (483)	Anemias (1,548)	Aortic aneurysm (2,706)	Aortic aneurysm (5,610)	Nutritional deficiencies (31,075)
20	SLE (18)/hernia (12)/suicide (12)	Diseases of the appendix (33)	Meningococcal infection (157)	Aortic aneurysm (416)	Pneumonitis (1,103)	Anemias (2,119)	SLE (5,495)/homicide (4,430)	Gallbladder disorders (24,676)
20+	–	–	–	–	–	–	–	SLE (10,238)

* There were 8 deaths from systemic lupus erythematosus (SLE) among those ages 0–4 years. Values in parentheses are the number of deaths.

† External injury causes of death.

SUBJECTS AND METHODS

We conducted a population-based study using nationwide mortality counts for all female residents of the US from 2000 to 2015. Data on SLE deaths were obtained from the CDC Wide-ranging OnLine Data for Epidemiologic Research (WONDER) Multiple Cause of Death database (3). Death certificates in the US provide the International Classification of Diseases (ICD) code for the underlying or contributing causes of death (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40512/abstract>). The underlying cause of death is defined as “the disease or injury that initiated the events resulting in death” (4). The contributing causes of death are defined as “other significant conditions contributing to death but not resulting in the underlying cause.” Deaths were attributed to SLE if an ICD-10 code for SLE (M32 [SLE], M32.1 [SLE with organ or system involvement], M32.8 [other forms of SLE], or M32.9 [SLE, unspecified]) was listed as an underlying or contributing cause of death on the death certificate.

Age, race, and ethnicity were ascertained using standard methods described in the CDC’s Vital Statistics technical appendix (5). Race was classified as white, black or African-American, Asian or Pacific Islander, or American Indian or Alaska Native. Ethnicity was classified as Hispanic or non-Hispanic.

Death counts were obtained, using WONDER, in the female population of the US by age groups and race/ethnicity. Data on the leading causes of death were obtained from the CDC WONDER Web-based Injury Statistics Query and Reporting System database (3).

RESULTS

During 2000–2015, there were a total of 28,411 deaths of females with SLE recorded as the underlying or a contributing cause of death. The largest number of SLE deaths was in the group ages 65 years and older (Table 1). There were 8 SLE deaths among those ages 0–4 years, 18 among those ages 5–9 years, and 78 among those ages 10–14 years.

The ranking of SLE deaths relative to the 20 official leading causes of death in females is displayed in Table 1. SLE is among the top 20 leading causes of death in females between 5 and 64 years of age. SLE ranked tenth among those ages 15–24 years, fourteenth among those ages 25–34 years and those ages 35–44 years, and fifteenth among those ages 10–14 years. In those ages 15–24 years, SLE was the number one cause of death among chronic inflammatory diseases, ranking higher than diabetes mellitus, HIV, chronic lower respiratory disease, nephritis, pneumonitis, and liver disease.

Since the SLE mortality rate is independently associated with female sex and nonwhite race (1), we assessed

the relative burden of SLE mortality in minority females of reproductive age (Figure 1). To focus on the organic causes of death, the 3 common external injury causes of death, namely, unintentional injury, homicide, and suicide, were excluded from this analysis. For females of all races/ethnicities, SLE ranked seventh as the leading cause of death among those ages 15–24 years and eleventh among both those ages 25–34 years and those ages 35–44 years. Among black and Hispanic females, the rankings for SLE were higher: fifth among those ages 15–24 years, sixth among those ages 25–34 years, and eighth or ninth among those ages 35–44 years.

DISCUSSION

This study illustrates that SLE is among the leading causes of death in young females. The actual rankings of SLE are likely even higher, because SLE may not be recorded on the death certificate for as many as 40% of patients with SLE in the US (6). Furthermore, the rankings of some other leading causes of death may be higher than their actual rank; for example, death certificates tend to overestimate cardiovascular disease mortality (7). The underreporting of SLE on death certificates may occur because patients with SLE die prematurely of complications such as cardiovascular events, infections, renal failure, and respiratory diseases (8). These proximate causes of death may be perceived to be unrelated to SLE, when in fact the disease or the medications used for it predispose to them. At the time of death, many SLE patients may be under the care of physicians who may have a limited awareness of SLE as the underlying cause of death. For example, 86% of 2,314 SLE deaths in Sweden occurred in hospital units other than rheumatology (9). Thus, many SLE patients may have only the proximate causes of death, and not SLE, recorded on their death certificates. Understanding the burden of SLE deaths will help improve this knowledge gap in health care workers. An awareness campaign to educate primary care physicians and internists about the multiorgan complications of SLE and its varying presentations at the time of death may be helpful in future studies to assess the true burden of SLE mortality.

We recently described a multiple regression analysis of SLE mortality risk stratified by race/ethnicity (1). That analysis showed that SLE mortality risk was higher in females than in men in all races/ethnicities, but both the adjusted odds ratio (OR) and predicted annual mortality differences were largest in African Americans, followed by Hispanics. The adjusted ORs for females relative to males were 6.49 (95% confidence interval [95% CI] 6.02–7.00) in African Americans, 5.81 (95% CI

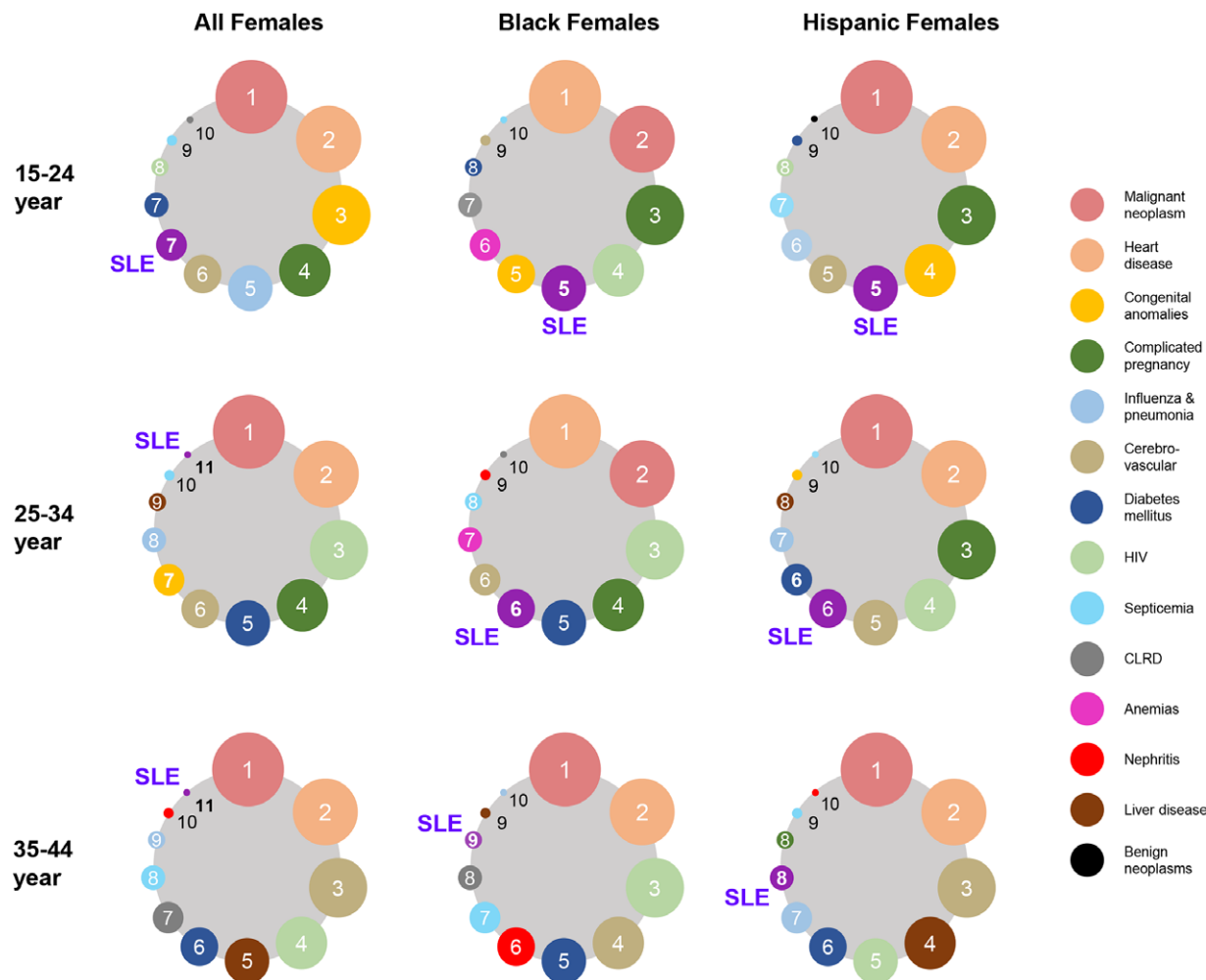


Figure 1. Leading causes of deaths of females of reproductive age by race/ethnicity and age. The ranking of systemic lupus erythematosus (SLE) relative to the 10 official leading causes of death in females of reproductive age in the US from 2000 to 2015 is shown. Rankings are shown for females of all races, non-Hispanic black females, and Hispanic females in each age group. SLE deaths include cases where SLE was listed as the underlying or contributing cause of death using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) code M32. (All deaths since 1999 have been coded using ICD-10.) To focus on the organic causes of death, we excluded the external injury causes of death, namely, unintentional injury, homicide, and suicide, from this analysis. CLRD = chronic lower respiratory disease.

5.19–6.51) in Hispanics, and 4.62 (95% CI 4.37–4.88) in whites. Consistently, SLE ranked higher among the leading causes of death in nonwhite females. Our data likely underestimate the true disease burden in minorities, given the underascertainment and underrecording of SLE deaths in less well-educated ethnic minorities (10) and uninsured patients (6). The higher rankings of SLE deaths in minority females are unlikely to be artifacts from misclassification of cause of death, because greater underreporting of SLE as the cause of death in underprivileged groups (6,10) would lead to greater underestimation of SLE deaths in the groups in which we found the ranking to be higher, namely African Americans and Hispanics. The difficulty in ascertaining the accuracy of the

physician's coding on death certificates still remains an important limitation of this study. However, it is less likely that SLE would be recorded as a cause of death on the death certificates of those who did not have SLE.

Several studies have suggested that older age is associated with lack of recording of SLE on death certificates. In the Lupus in Minorities, Nature versus nurture (LUMINA) and Carolina Lupus Study cohorts, age at death was significantly higher among those for whom SLE was omitted on the death certificate compared to those who had SLE included on the death certificate (mean $\pm$ SD 50.9 $\pm$ 15.6 years versus 39.1 $\pm$ 18.6 years; $P = 0.005$; $n = 76$ SLE deaths) (6). The age at death was also significantly higher for SLE decedents who did not have SLE

recorded on the death certificate compared to those who did in the Georgia Lupus Registry (mean $\pm$ SD 55.5 $\pm$ 16.4 years versus 44.4 $\pm$ 17.6 years; $P < 0.0001$; $n = 321$ SLE deaths) (11). In a Swedish population-based study that included 1,802 SLE deaths, decedents 60–79 years old at death were ~ 2.5 times as likely to have SLE missing from their death certificates than those younger than 40 years (OR 2.48 [95% CI 1.34–4.58]) (12). Those studies also found that SLE patients who died of cancer or a cardiovascular event were more likely to be in the unrecorded group (6,12). Thus, the lower placement of SLE in the ranking of leading causes of death in older age groups may be due to omission of SLE on the death certificates of SLE decedents whose proximate causes of death were cancer or cardiovascular events.

Our findings underscore that SLE is an important public health issue among young females, which should be addressed by targeted public health and research programs. Increasing awareness among pediatricians and primary care physicians about the importance of early diagnosis and better management of SLE may help to reduce the high burden of SLE mortality. In recognition of the high mortality of SLE, in 2016 the National Institutes of Health increased research funding for SLE to \$97 million annually. This is in comparison to \$1,084 million for diabetes mellitus and \$3,780 million for HIV (13). In light of our data showing a higher burden of SLE mortality in younger females than previously perceived, further increases in research funding for SLE are warranted.

In conclusion, the inclusion of SLE in the CDC's selected list of causes of death for the annual ranking would highlight the importance of this disease as a major cause of death in young females. The recognition of SLE as a leading cause of death may influence physicians' coding on death certificates, CDC reporting of death burden, government policy, and government research funding, which may eventually help to reduce the disease burden of SLE.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved

the final version to be published. Dr. Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Yen, Singh.

Acquisition of data. Yen, Singh.

Analysis and interpretation of data. Yen, Singh.

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