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Lupus – An Unrecognized Leading Cause of Death in Young Women: Population-based Study Using Nationwide Death Certificates, 2000–2015

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Abstract

Objective—Mortality statistics from the Centers for Disease Control and Prevention (CDC) is used for planning healthcare policy and allocating resources. CDC uses this data to compile its annual leading-causes-of-death ranking based on a selected list of 113 causes. SLE is not included on this list. Since the cause-of-death ranking is a useful tool for assessing the relative burden of cause-specific mortality, we ranked SLE deaths among CDC’s leading causes-of-death to see whether SLE is a significant cause of death among women.

Methods—Death counts were obtained from the CDC’s Wide-ranging Online Data for Epidemiologic Research database in U.S. female population, 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 to 2015, there were 28,411 female deaths with SLE recorded as the underlying or contributing causes of death. SLE ranked among the top 20 leading-causes-of-death in females between 5 and 64 years of age. SLE ranked 10th in the 15–24 years, 14th in the 25–34 and the 35–44 years, and 15th in the 10–14 years age groups. Among black and Hispanic females, SLE ranked 5th in the 15–24 years, 6th in the 25–34 years, and 8th–9th in the 35–44 years age groups, after excluding the three common external injury causes of death from analysis.

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

Introduction

Systemic lupus erythematosus (SLE) is a predominately female, chronic inflammatory disease that can affect virtually any organ. We recently analyzed secular trends and

population characteristics associated with SLE mortality using the United States (U.S.) nationwide mortality database comprising of 62,843 SLE deaths, of which 84% were in women (1). We found that although rates of SLE mortality have decreased over the past five decades, SLE mortality rates remain high relative to mortality rate for all causes other than SLE (non-SLE). In fact, the ratio of SLE mortality rate to the mortality rate for non-SLE causes was 34.6% higher in 2013 than in 1968. Thus, SLE mortality remains high in the U.S. population.

The Centers for Disease Control and Prevention (CDC)'s National Vital Statistics System 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 deaths of U.S. 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 U.S. population and are used to estimate the burden of specific diseases. Mortality statistics are also used for healthcare policy planning and resource allocation.

Using the National Vital Statistics System mortality database, CDC compiles its 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 CDC's leading causes-of-death to determine the relative burden of SLE deaths in women.

Methods

This is a population-based study using nationwide mortality counts for all female U.S. residents from 2000–2015. Data on SLE deaths were obtained from the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause-of-Death database (3).

Death certificates in the U.S. provide the International Classification of Diseases (ICD) code for the *underlying* or *contributing* causes of death (Appendix Figure 1). The underlying cause of death is defined as “the disease or injury that initiated the events resulting in death” (4). The *contributing* cause of death is 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], and M32.9 [SLE, unspecified]) was listed as the underlying or contributing causes of death on the death certificates.

Age, race, and ethnicity were ascertained using standard methods described in the Technical Appendix, Vital Statistics (5). Race is classified as white, black or African-American, Asian or Pacific Islander, and American Indian or Alaska Native. Ethnicity is classified as Hispanic or Non-Hispanic.

Death counts were obtained, using WONDER, in female U.S. population 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 (WISQARS) database (3).

Results

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

The ranking of SLE deaths relative to the official 20 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 10th in the 15–24 years age group, 14th in the 25–34 and the 35–44 years age groups, and 15th in the 10–14-year age group. In the 15–24 years age group, SLE is the #1 single chronic inflammatory disease, ranking higher than diabetes mellitus, human immune deficiency virus disease, chronic lower respiratory disease, nephritis, pneumonitis, and liver diseases.

Since SLE mortality rate is independently associated with female gender and non-White races (1), we assessed the relative burden of SLE mortality in minority women of reproductive age (Figure 1). To focus on the organic causes of death, three common external injury causes of death, namely unintentional injury, homicide, and suicide, were excluded from this analysis. For females of all race/ethnicity, SLE ranked 7th as the leading cause of death in the 15–24 years age group and 11th in both the 25–34 and 35–44 years age groups. Among Black and Hispanic females, the rankings for SLE were higher: 5th in the 15–24 years age group, 6th in the 25–34 years age group, and 8th–9th in the 35–44 years age group.

Discussion

This study illustrates that SLE is among the leading causes of death in young women. The actual rankings for SLE would likely be even higher, because SLE may not be recorded on the death certificates in as many as 40% of patients with SLE in the U.S. (6). Furthermore, the ranking for 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 the 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 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 only have 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 healthcare workers. An awareness campaign to educate primary care physicians and internists about the multi-organ 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 reported the multiple regression analysis of SLE mortality risk stratified by race/ethnicity (1). This showed that SLE mortality risk was higher in females than in males in all race/ethnic groups, but both the adjusted odds ratio and predicted annual mortality differences were largest in black persons followed by Hispanics. The adjusted odds ratios for females relative to males were 6.49 (95% CI, 6.02 to 7.00) in black persons, 5.81 (95% CI, 5.19 to 6.51) in Hispanics, and 4.62 (95% CI, 4.37 to 4.88) in white persons. Consistently, SLE ranked higher among the leading causes of death in non-white women. Our data likely underestimate the true disease burden in minorities, given the under-ascertainment and under-recording of SLE deaths in less-well educated ethnic minorities (10) and uninsured patients (6). The higher rankings for SLE deaths in minority women 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 we found the ranking to be higher, namely black persons and Hispanics. The difficulty in ascertaining the accuracy of the physicians' coding on death certificates still remains an important limitation of this study. Though, it is less likely that SLE would be recorded as a cause of death on death certificates of the deceased who did not have SLE.

Several studies have suggested that older age is associated with lack of recording of SLE in death certificates. In the LUMINA (Lupus in Minorities: Nature vs Nurture) and Carolina Lupus Study cohorts, the age at death was significantly higher among those for whom SLE was omitted on the death certificates compared to those who had SLE included in death certificates (mean \pm S.D., 50.9 \pm 15.6 versus 39.1 \pm 18.6; $P = 0.005$; $n =$ total 76 SLE deaths) (6). The age at death was also significantly higher for SLE decedents who did not have SLE recorded on the death certificates compared to those who had (mean \pm S.D., 55.5 \pm 16.4 versus 44.4 \pm 17.6; $P < 0.0001$; $n = 321$ SLE deaths) in the Georgia Lupus Registry (11). In a Swedish population-based study that included 1,802 SLE deaths, decedents 60–79 years old at death were approximately 2.5 times as likely to have SLE missing from their death certificates compared with those <40 years (odds ratio: 2.48, 95% CI: 1.34–4.58) (12). These studies also found that SLE patients dying of cancer or a cardiovascular event were more likely to be in the non-recorded group (6, 12). Thus, the lower placement of SLE in the leading-causes-of-death ranking list in older age groups may be due to omission of SLE on death certificates of SLE decedents whose proximate causes of death were cancer and cardiovascular events.

Our findings underscore SLE as an important public health issue in young women, 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, the National Institutes of Health in 2015 increased funding for SLE to 90 million research dollars annually. This is in comparison to 1,010 million for diabetes mellitus and 3,166 million dollars for human immune deficiency virus disease. In light of our data showing a higher burden of SLE mortality in younger women than previously perceived, further increases in research funding for SLE is warranted.

In conclusion, the inclusion of SLE in CDC's selected list of causes of death for their annual ranking would highlight the importance of this disease as a major cause of death among young women. 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 in reducing the disease burden of SLE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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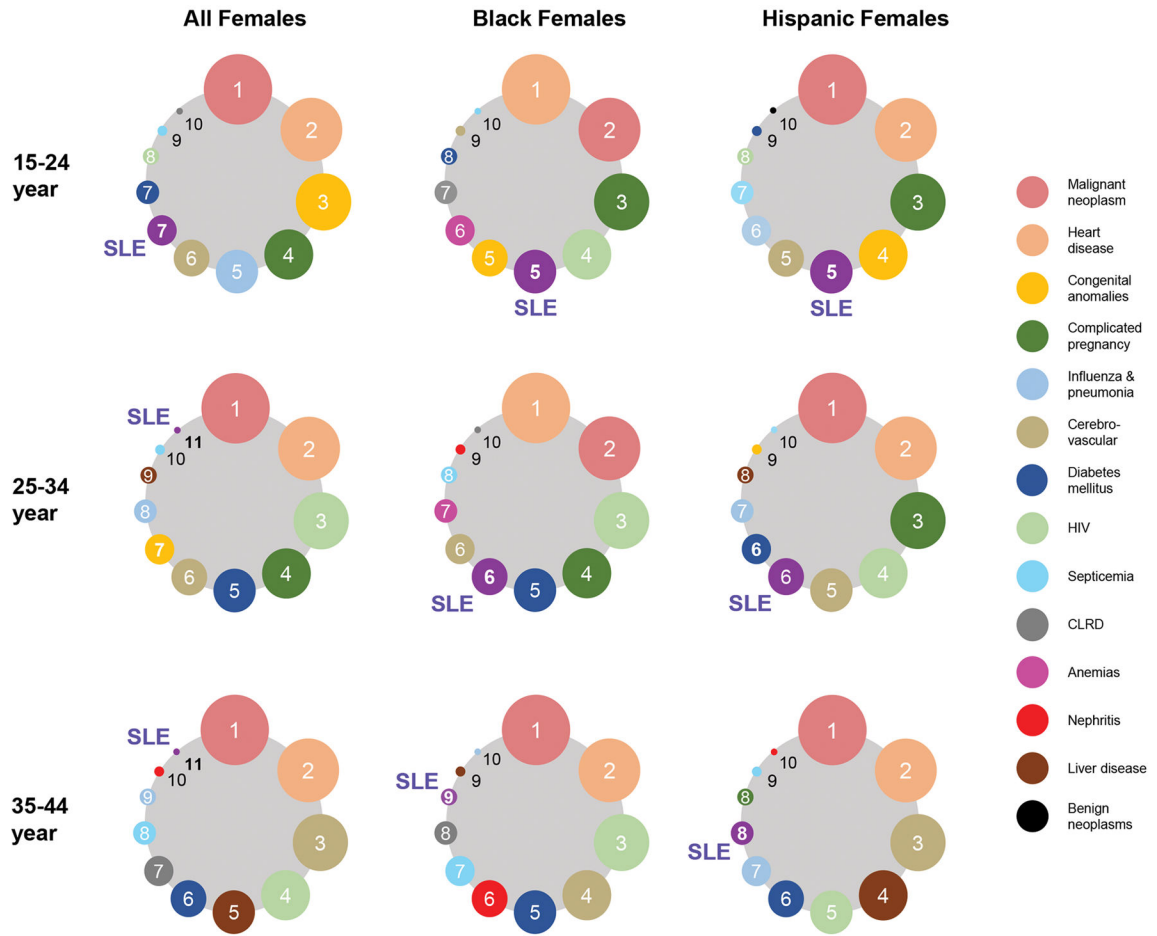


Figure 1. Leading Causes of Deaths for Females of Reproductive Age by Race/Ethnicity and Age
 The ranking of SLE relative to the official 10 leading causes of death in women of reproductive age in the United States from 2000–2015 is displayed. SLE deaths include cases where SLE was listed as the underlying or contributing cause of death using 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. Ranking is shown for women of all races (*left panels*), non-Hispanic Black (*middle*), and Hispanic women (*right*) in 15–24-year (*top*), 25–34-year (*middle*), and 35–44-year (*bottom*) age groups. ICD, International Classification of Diseases.

Table 1

Twenty leading causes of death in females in the United States from 2000 to 2015.

Rank	5-9 year *	10-14 year	15-24 year	25-34 year	35-44 year	45-54 year	55-64 year	65+ year
1								
2	Malignant Neoplasms 3,415	Malignant Neoplasms 3,450		Malignant Neoplasms 30,101	Malignant Neoplasms 121,604	Malignant Neoplasms 387,239	Malignant Neoplasms 747,302	Heart Diseases 4,468,532
3	Congenital Anomalies 1,420				Heart Diseases 57,325	Heart Diseases 166,833	Heart Diseases 334,259	Malignant Neoplasms 3,046,099
4		Congenital Anomalies 1,302	Malignant Neoplasms 10,454	Heart Diseases 16,951		Cerebrovascular 42,810	Chronic Lower Resp Disease 104,733	Cerebrovascular 1,224,648
5	Heart Diseases 726		Heart Disease 5,534		Cerebrovascular 15,801	Liver Diseases 38,999	Diabetes Mellitus 75,872	Chronic Lower Resp Disease 978,817
6	Influenza & Pneumonia 408	Heart Diseases 951	Congenital Anomalies 2,820	HIV 6,543	HIV 15,224	Diabetes Mellitus 35,350	Cerebrovascular 73,651	Alzheimer's Disease 844,609
7	Chronic Lower Resp Disease 337	Chronic Lower Resp Disease 451	Complicated Pregnancy 2,502	Complicated Pregnancy 5,193	Liver Disease 14,919	Chronic Lower Resp Dis 33,297	Liver Disease 41,614	Diabetes Mellitus 454,459
8	Benign Neoplasms 333	Influenza & Pneumonia 420	Influenza & Pneumonia 1,358	Diabetes Mellitus 4,329	Diabetes Mellitus 12,094		Septicemia 32,722	Influenza & Pneumonia 448,129
9	Cerebrovascular 299	Cerebrovascular 339	Cerebrovascular 1,357	Cerebrovascular 4,097		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 Resp Disease 6,948	Influenza & Pneumonia 14,323	Influenza & Pneumonia 24,855	Septicemia 243,733
11	Anemias 136	Septicemia 260	HIV 1,060	Influenza & Pneumonia 2,888	Septicemia 6,671	HIV 13,935		Hypertension 216,273
12	Perinatal Period 122	Diabetes Mellitus 180	Septicemia 1,023	Liver Disease 2,674	Influenza & Pneumonia 6,505	Nephritis 13,665	Hypertension 15,010	Parkinson's Disease 136,101
13	Meningitis 66	Anemias 158	Chronic Lower Resp 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 Resp Disease 2,000	SLE 3,646 Congenital Anomalies 3,502		Benign Neoplasms 9,587	Benign Neoplasms 93,021

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	5-9 year *	10-14 year	15-24 year	25-34 year	35-44 year	45-54 year	55-64 year	65+ year
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 Diseases 76,262
17	Diseases of 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 Diseases 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 Appendix 33	Meningococcal Infection 157	Aortic Aneurysm 416	Pneumonitis 1,103	Anemias 2,119	SLE 5,495	Gallbladder Disorders 24,676
20+								SLE 10,238

Abbreviations: HIV, human immune deficiency virus disease; Resp, Respiratory.

* There were 8 SLE deaths in 0-4-year age group (not shown in the table).

† External injury causes of death, including unintentional injury, homicide, and suicide, are represented in the gray font. SLE is shown in the shaded cells.