PURPOSE To map the magnitudes and temporal trends of chronic myeloid leukemia (CML) along with its attributable risk factors, providing the essential foundation for targeted public policies at the national, regional, and global levels.

MATERIALS AND METHODS We retrieved annual data on CML burden in 204 countries and regions from the Global Burden of Disease Study 2019 in 1990-2019. The estimated annual percentage change (EAPC) was calculated to quantify the temporal trends of CML burden by region, sex, and age group.

RESULTS Globally, the age-standardized incidence rate of CML declined weakly over the past few years (EAPC: −1.04), but the number of incident cases increased by 54.1% to 65.8 × 10^3 in 2019. By contrast, a dramatic drop in death and disability-adjusted life years (DALYs) rate (EAPCs: −2.55; −2.69) led to a reduction in deaths and DALYs, especially in high-income regions. In 2019, the highest age-standardized death rate was observed in Ethiopia (1.89 per 100,000). The death rate of CML was pronounced among the population age above 70 years. DALYs of CML worldwide were primarily attributable to smoking (12.2%), high body mass index (5.0%), occupational exposure to benzene (0.9%), and occupational exposure to formaldehyde (0.3%) in 2019.

CONCLUSION Although the mortality rate of CML has decreased significantly, the management of patients with CML cannot be neglected, especially in elders and developing regions.

INTRODUCTION Chronic myeloid leukemia (CML), a myeloproliferative disorder originating in the hematopoietic stem-cell compartment, is characterized by a fused oncogene called BCR-ABL1 on the Philadelphia chromosome, which resulted from a reciprocal t(9;22) chromosomal translocation.1,2 The global incidence rate of CML was close to one case in 100,000 population in 2018, and it accounts for approximately 15% of newly diagnosed cases of leukemia in adults.3 The natural history of CML has a triphasic clinical course comprising an initial chronic phase, an accelerated phase, and a blast phase.4-6 CML is usually diagnosed in chronic phase,7 which without effective medical intervention will convert to a blast crisis.8

Before 2000, drug therapy was limited to nonspecific agents such as busulfan, hydroxyurea, and interferon alfa for CML.9 The appearance of tyrosine kinase inhibitor (TKI) was a milestone for the treatment of CML. According to the reports of American Cancer Society, the current 5-year relative survival rate for adults is 69% for CML, tripled than the mid-1970s (about 22%).10 The annual fatality rate changed to 1%-2% after 2000 from 10% to 20%.3,11 A previous study indicated that the estimated prevalence of CML is approximately 144,000 in 2030, 167,000 in 2040, and 181,000 in 2050, when it will reach a near plateau prevalence.12 Under such a large CML patient population, how should global or regional health policymakers allocate limited health resources is a major challenge. Furthermore, scattered article reported some risk factors related to CML’s morbidity and mortality, such as exposure to high-level ionizing radiation, chemotherapy, and genetic abnormalities.1,13-15 But systematic analysis is lacking. In our study, we analyzed the changing trend of incidence, mortality, and disability-adjusted life years (DALYs) of CML from 1990 to 2019 on the basis of the Global Burden of Diseases, Injuries, and Risk factor Study 2019 (GBD 2019), which provides a systematic scientific assessment of published, publicly available, and contributed data on incidence, prevalence, mortality, and DALYs because of 369 diseases and injuries, for two sexes, and 204 countries and territories.16 Moreover, we provide the potential risk factors attributed to
Globally, the incident cases of CML increased by 54.1% to $65.8 \times 10^3$ in 2019; however, a dramatic drop in death rate (estimated annual percentage changes: $-2.55$) led to a reduction in deaths, which resulted in an increasing prevalence. The death rate of CML was pronounced among the population age above 70 years. Disability-adjusted life years of CML worldwide were primarily attributable to smoking (12.2%), high body mass index (5.0%), occupational exposure to benzene (0.9%), and occupational exposure to formaldehyde (0.3%) in 2019.

Relevance
Low-income countries need more health assistance to meet the treatment needs. Patients’ management is important in high-income countries because of heavier burden of CML. Smoking control should be taken actively.

CML-related DALYs. Our results would provide a systematical evidence-based reference for the prevention and treatment management for CML.

MATERIALS AND METHODS
Data Source
The detailed data processing steps and modeling estimations of CML burden in GBD 2019 have been delineated in previous GBD studies, and here, we briefly introduce the methods specific to the estimation of CML burden. Each step performed in this study to analyze and report the global CML burden complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statements. The original data sources for CML burden estimation in GBD 2019 study resulted from individual cancer registries or aggregated databases of cancer registries, such as Cancer Incidence in Five Continents (CI5), and SEER in the United States. Moreover, GBD 2019 used all data from GBD 2017 and added registry data from other 14 countries, including Argentina, Australia, Austria, etc. The detailed modeling flow and codes for the estimation of CML burden could be found from the accessible supporting website. We retrieved annual data on CML burden by sex and 5-year age group in 204 countries and regions from 1990 to 2019 from the Institute for Health Metrics and Evaluation. To describe the geographic distribution of CML burden across the world, the 204 available countries and territories were divided into 21 GBD regions, which were further simplified into seven super GBD regions. The sociodemographic index (SDI), a comprehensive indicator, was calculated by combining per capita income, years of education, and fertility to reflect the development level of health, which was used to categorize the world into five regions (Table 1).

The comparative risk assessment framework was applied to assess the contribution from potential risk factors for CML burden: (1) to identify risk-outcome pairs with convincing or probable evidence; (2) to summarize the relative risk on the basis of the metaregression; (3) to estimate the population exposure levels and geographic distributions using spatiotemporal Gaussian regression, Bayesian metaregression, and other methods; (4) to define the lowest limitation of risk exposure level; (5) to calculate the population attributable fractions and attributable burden; and (6) to estimate population attributable fractions of combinations of risk factors by considering the mediation of different risk factors. Among 87 risk factors quantified in GBD 2019, the attributable risks from smoking, high body mass index, occupational exposure to benzene, and occupational exposure to formaldehyde for CML burden were well-estimated.

Statistical Analysis
The age-standardized incidence rate (ASIR), age-standardized death rate (ASDR), and age-standardized rate of DALYs (ASR of DALYs) were used to quantify the variation of CML burden by calendar year, sex, and region, to avoid the differences in the age composition of the population. We calculated the estimated annual percentage change (EAPC) to describe the temporal trend in various ASRs of CML burden. We performed a regression model to fit the natural logarithm of the ASR with the calendar year, namely, $\ln \text{(ASR)} = \alpha + \beta \times \text{calendar year} + \epsilon$. The EAPC with its 95% CI was estimated according to the formula $100 \times (\exp(\beta) - 1)$. We applied the Spearman rank to calculate the correlation between the EAPCs in CML burden and the baseline burden in 1990 and the SDI in 2019 at the national level. All statistical analyses in the current study were conducted using R program version 4.0.3, and the two-sided $P$ value $< .05$ was considered statistically significant.

RESULTS
Global Burden of CML
Globally, the incident cases of CML were increased dramatically by 54.1% in the past 30 years from $42.7 \times 10^3$ in

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| Characteristics | Incidence Cases No. × 10^3 (95% UI) | ASIR per 100,000 No. (95% UI) | Incidence Cases No. × 10^3 (95% UI) | ASIR per 100,000 No. (95% UI) | EAPC in ASIR No. (95% CI) |
|-----------------|-----------------------------------|-------------------------------|-----------------------------------|-------------------------------|--------------------------|
| Overall         | 42.7 (34.52 to 56.19)             | 0.96 (0.82 to 1.19)           | 65.8 (59.45 to 74.13)             | 0.83 (0.75 to 0.94)           | −1.04 (−1.33 to −0.76)   |
| Sex             |                                   |                               |                                   |                               |                          |
| Male            | 23.71 (17.43 to 33.11)            | 1.14 (0.91 to 1.46)           | 36.22 (31.97 to 41.96)            | 0.99 (0.87 to 1.15)           | −0.93 (−1.17 to −0.69)   |
| Female          | 18.99 (14.54 to 23.98)            | 0.82 (0.65 to 0.99)           | 29.58 (25.96 to 33.96)            | 0.7 (0.61 to 0.8)             | −1.21 (−1.53 to −0.88)   |
| GBD region      |                                   |                               |                                   |                               |                          |
| Southern Latin America | 1.95 (1.78 to 2.26)           | 1.01 (0.92 to 1.17)           | 4.26 (3.54 to 5.1)               | 1.24 (1.04 to 1.47)           | 0.51 (0.39 to 0.64)      |
| High-low SDAI   | 5.1 (4.76 to 5.42)               | 1.51 (1.41 to 1.6)           | 6.19 (5.31 to 7.23)              | 1.04 (0.89 to 1.2)            | −2.03 (−2.42 to −1.63)  |
| Western Europe  | 9.97 (9.18 to 10.74)             | 1.93 (1.78 to 2.08)           | 24.13 (20.47 to 29.3)            | 2.97 (2.54 to 3.56)           | 0.31 (−0.43 to 1.06)    |
| Australasia     | 0.32 (0.28 to 0.35)              | 0.18 (0.15 to 0.21)           | 0.53 (0.4 to 0.71)               | 0.82 (0.72 to 0.93)           | −1.56 (−1.85 to −1.27)  |
| Tropical Latin America | 0.7 (0.67 to 0.76)             | 0.63 (0.6 to 0.68)           | 0.64 (0.59 to 0.72)              | 0.27 (0.25 to 0.3)            | −3.4 (−3.78 to −3.02)   |
| Andean Latin America | 0.09 (0.07 to 0.12)             | 0.34 (0.27 to 0.42)           | 0.19 (0.15 to 0.24)              | 0.33 (0.25 to 0.41)           | 0.28 (0.09 to 0.46)     |
| Central Latin America | 0.53 (0.49 to 0.55)             | 1.89 (0.45 to 0.51)           | 0.84 (0.7 to 1.01)               | 0.35 (0.29 to 0.42)           | −1.65 (−1.87 to −1.44)  |
| South Asia      | 0.37 (0.33 to 0.42)              | 0.81 (0.71 to 0.9)           | 0.32 (0.25 to 0.4)               | 0.39 (0.31 to 0.5)            | −3.15 (−3.5 to −2.79)   |
| Caribbean       | 0.25 (0.2 to 0.37)               | 0.83 (0.69 to 1.13)           | 0.31 (0.25 to 0.39)              | 0.62 (0.49 to 0.79)           | −0.96 (−1.11 to −0.81)  |
| South Asia      | 9.93 (6.17 to 15.33)             | 1.15 (0.84 to 1.58)           | 11.12 (9.27 to 13.39)            | 0.7 (0.58 to 0.85)            | −1.95 (−2.07 to −1.83)  |
| Southeast Asia  | 1.24 (0.89 to 1.65)              | 0.37 (0.28 to 0.47)           | 1.96 (1.62 to 2.44)              | 0.31 (0.26 to 0.38)           | −0.62 (−0.68 to −0.55)  |
| East Asia       | 1.59 (1.13 to 2.02)              | 0.15 (0.11 to 0.19)           | 3.91 (3.27 to 4.82)              | 0.22 (0.18 to 0.26)           | 0.10 (0.54 to 1.54)     |
| Oceania         | 0.02 (0.02 to 0.04)              | 0.59 (0.41 to 0.8)           | 0.04 (0.03 to 0.06)              | 0.43 (0.29 to 0.61)           | −1.26 (−1.37 to −1.15)  |
| Western Sub-Saharan Africa | 0.55 (0.41 to 0.72)             | 0.43 (0.35 to 0.53)           | 1.12 (0.89 to 1.4)               | 0.41 (0.33 to 0.51)           | −0.06 (−0.11 to −0.01)  |
| Eastern Sub-Saharan Africa | 4.53 (1.55 to 11.1)            | 2.45 (1.29 to 4.93)           | 3.19 (2.04 to 4.7)               | 1.16 (0.77 to 1.62)           | −2.74 (−2.87 to −2.61)  |
| Central Sub-Saharan Africa | 0.25 (0.12 to 0.59)             | 0.55 (0.38 to 0.91)           | 0.32 (0.22 to 0.46)              | 0.39 (0.26 to 0.58)           | −1.01 (−1.19 to −0.83)  |
| Southern Sub-Saharan Africa | 0.04 (0.03 to 0.05)             | 0.1 (0.08 to 0.13)           | 0.05 (0.04 to 0.07)              | 0.08 (0.06 to 0.1)            | −1.06 (−1.28 to −0.85)  |

Abbreviations: ASIR, age-standardized incidence rate; EAPC, estimated annual percentage change; GBD, Global Burden of Disease; UI, uncertainty interval; SDI, sociodemographic index.

The global deaths of CML decreased slightly during this period, with 31.07 × 10^3 deaths in 1990 and 29.93 × 10^3 deaths in 2019, whereas the ASDR decreased significantly by 2.55% per year (Table 2). In terms of sex, the number of male deaths was more than that of female deaths, with a slight decrease with the EAPC of −1.04 (Table 1). Males were more likely to suffer from CML than females, and the male-female ratio was 1.2 in 2019 (Table 1 and Data Supplement).
ratio of 1.5 in 2019. Females’ ASDR decreased slightly faster than males’ ASDR (Table 2 and Data Supplement).

The DALYs of CML decreased to 104.97 ×10^4 in 2019 from 134.44 ×10^4 in 1990, and the ASR of DALYs was decreased by 2.69% per year. Similar to the changing trend of death, females had an advantage over males both in DALYs and in EAPC of ASR of DALYs (Data Supplement).

Regional and National Burden of CML

High SDI regions accounted for nearly half of the global CML incident cases and had the highest ASIR, which was 2.1-5 times higher than other four SDI regions in 2019. All SDI regions presented a significant decrease in ASIR of CML in both sexes, especially in the low SDI region (Table 1 and Data Supplement). Regarding the GBD regions, the ASIR in most regions (16 of 21) showed a downward trend (Table 1). Both the largest incident cases and highest ASIR appeared in Western Europe (Table 1 and Figs 1A and 1C). Thereinto, Germany had the most incident cases and the highest ASIR, which was 2.1-5 times higher than other four SDI regions in 2019. All SDI regions had the highest ASIR (Data Supplement) with a negative EAPC. The fastest increased ASIR occurred in Cyprus (Data Supplement).

For mortality trend, high or high-middle SDI regions presented better progress in CML treatment, as evidenced by a significant reduction in the number and rate of DALYs (Data Supplement). Almost all SDI and GBD regions had a significant downward trend in ASDR (except for Andean Latin America and Western Sub-Saharan Africa)/ASR of DALYs of CML after 2000, especially in high SDI regions (Table 2, Data Supplement, Figs 1B and 1D, Data Supplement). Joinpoint analysis revealed that both ASDR and ASR of DALYs showed exaggerated decline around 2000. Specifically in high SDI regions, the annual percentage changes were −7.502 in ASDR and −8.100 in ASR of DALYs during 1998-2005 (Data Supplement). At the national level, India had the most deaths and DALYs all over the world (Data Supplement). Although Ethiopia ranked first in the ASDR and ASR of DALYs (Data Supplement), Jamaica had the most rapid growth in ASDR, followed by Zimbabwe and El Salvador (Data Supplement). Lesotho and Jamaica were the top two in ASR of DALYs, and this rate increased quicker than 3% per year (Data Supplement). Key data of mortality and morbidity of each country are given in the Data Supplement.

The Correlation Between SDI and CML Burden

Overall, the EAPC of ASIR was negatively correlated with ASIR in 1990 (Fig 2A). The negative relationship between EAPC of ASDR/ASR of DALYs and the ASDR/DALYs rate in 1990 was pronounced (Fig 2B and Data Supplement). We found a positive correlation coefficient between SDI in 2019 and the EAPC of ASIR at national levels, which was only limited in the countries where SDI > 0.7 (Fig 2C). By contrast, the countries with higher SDI usually presented a faster decline between SDI and EAPC of ASIR, especially when the SDI was > 0.6 (Fig 2D and Data Supplement).

Furthermore, we investigated the annual change trend in ASIR, ASDR, and ASR of DALYs with SDI increasing in 21 GBD regions. The ASIR decreased slightly with the SDI < 0.63, but a positive relationship was presented when SDI was greater than this value. The ASDR and ASR of DALYs in most GBD regions had a dramatically negative correlation with SDI, especially in regions with high SDI (Data Supplement).

The Age Decomposition of CML Burden

Patients aged 70-84 years accounted for a larger proportion in incident and death cases, especially in the high SDI regions (Figs 3A and 3B), but no obvious change in deaths (Data Supplement). Males above 70 years old always had the highest ASIR and ASDR in the past 30 years. The death rate in high or high-middle SDI regions showed a downward trend fortunately (Data Supplement). Children who were affected by CML might be likely to go to DALYs in age 1-4 years (Fig 3C). Different from incidence and death, a wide scope of age from 25 to 69 years had an equal proportion in DALY number (Fig 3C). It was a remarkable fact that the ASR of DALYs and number of DALYs in children < 5 years old accounted for a large proportion in low SDI regions in the early years. This situation has been improved in recent years (Data Supplement).

The Risk Factors Associated With CML

On the basis of GBD 2019, four risk factors associated with CML were identified, including smoking (12.2%), high body mass index (5%), occupational exposure to benzene (0.9%), and occupational exposure to formaldehyde (0.3%). We found that smoking was the greatest contributor to CML-related DALYs for two sexes at both the global and regional level, especially in males. This phenomenon was more severe in high SDI regions. At the same time, high body mass should be taken seriously because subgroup analysis of the GBD geographic zone suggested that the ratio of high body mass index accounted for an increasing proportion of all risk factors (Fig 4 and Data Supplement). Until 2019, the proportion of high body mass in females had equal proportion with smoking in many areas, even exceeded smoking in five SDI regions except high SDI (Fig 4).

DISCUSSION

CML has become a chronic disease with a good prognosis. A study in 2016 reported that 50% of patients with CML die not from CML itself, but from secondary cancers and cardiovascular events. To our knowledge, our study is the latest to report the global burden of CML across 204 countries and territories from 1990 to 2019. It also provides health management strategies for different countries and regions, such as resolving the economic question of TKI in low or low-middle regions. With the application of TKI, CML DALYs decreased by 21.9% roughly from 1990 to 2019. This change was most
obvious around 2000, and especially in the high SDI areas with adequate TKI access, the mortality rate showed an obvious and rapid decline, whereas the areas without access to TKI showed a lag. Patients are rarely discontinued because of adverse reactions to TKI, so TKI adverse events do not have a significant effect on the median age of CML. At the same time, the incident cases increased by 54.1%, which will aggravate the burden of treatment. Under this situation, Western Europe had the largest incident cases and most rapid increasing ASDR/ASR of DALYs, which lead to a more difficult treatment and management work for local government. Furthermore, low SDI regions had the most cases and highest ASR of deaths and DALYs, which have improved in recent years. The possible reason might be that (1) higher levels of ionizing radiation and other pollutants in these developing countries, (2) delayed diagnosis and poor availability of TKI because of worse health services and lower economics, and (3) inadequate health registration.

| Characteristics | 1990 | 2019 | 1990-2019 |
|-----------------|------|------|-----------|
|                  | Death Cases | No. × 10³ (95% UI) | ASMR per 100,000 No. (95% UI) | Death Cases | No. × 10³ (95% UI) | ASMR per 100,000 No. (95% UI) | EAPC in ASMR No. (95% CI) |
| Overall         | 31.07 (25 to 41.33) | 0.71 (0.6 to 0.89) | 29.93 (27.01 to 33.48) | 0.38 (0.34 to 0.42) | 103 (95% UI) | 0.71 (0.6 to 0.89) | 29.93 (27.01 to 33.48) | 0.38 (0.34 to 0.42) | 103 (95% UI) | 2.65 to 3.75 |
| Sex             |                  |                  |                        |                  |                  |                  |                        |                  |                  |                  |
| Male            | 17.78 (12.9 to 24.74) | 0.88 (0.69 to 1.13) | 18.26 (15.58 to 21.34) | 0.49 (0.42 to 0.57) | 103 (95% UI) | 0.88 (0.69 to 1.13) | 18.26 (15.58 to 21.34) | 0.49 (0.42 to 0.57) | 103 (95% UI) | 2.65 to 3.75 |
| Female          | 13.28 (9.76 to 17.11) | 0.57 (0.44 to 0.71) | 11.67 (10.14 to 13.38) | 0.28 (0.24 to 0.32) | 103 (95% UI) | 0.57 (0.44 to 0.71) | 11.67 (10.14 to 13.38) | 0.28 (0.24 to 0.32) | 103 (95% UI) | 2.65 to 3.75 |
| SDI regions     |                  |                  |                        |                  |                  |                  |                        |                  |                  |                  |
| High SDI        | 7.94 (7.47 to 8.54) | 0.79 (0.75 to 0.85) | 4.81 (4.29 to 5.63) | 0.26 (0.23 to 0.3) | 103 (95% UI) | 0.79 (0.75 to 0.85) | 4.81 (4.29 to 5.63) | 0.26 (0.23 to 0.3) | 103 (95% UI) | 2.65 to 3.75 |
| High-middle SDI | 5.8 (5.34 to 6.16) | 0.54 (0.5 to 0.58) | 4.97 (4.55 to 5.51) | 0.26 (0.24 to 0.29) | 103 (95% UI) | 0.54 (0.5 to 0.58) | 4.97 (4.55 to 5.51) | 0.26 (0.24 to 0.29) | 103 (95% UI) | 2.65 to 3.75 |
| Middle SDI      | 4.73 (3.9 to 5.53) | 0.38 (0.32 to 0.43) | 6.65 (5.92 to 7.66) | 0.27 (0.24 to 0.31) | 103 (95% UI) | 0.38 (0.32 to 0.43) | 6.65 (5.92 to 7.66) | 0.27 (0.24 to 0.31) | 103 (95% UI) | 2.65 to 3.75 |
| Low-middle SDI  | 6.87 (4.47 to 10.28) | 0.82 (0.61 to 1.1) | 7.96 (6.62 to 9.75) | 0.54 (0.45 to 0.65) | 103 (95% UI) | 0.82 (0.61 to 1.1) | 7.96 (6.62 to 9.75) | 0.54 (0.45 to 0.65) | 103 (95% UI) | 2.65 to 3.75 |
| Low SDI         | 5.71 (2.73 to 11.83) | 1.34 (0.86 to 2.26) | 5.51 (4.07 to 6.95) | 0.79 (0.58 to 0.97) | 103 (95% UI) | 1.34 (0.86 to 2.26) | 5.51 (4.07 to 6.95) | 0.79 (0.58 to 0.97) | 103 (95% UI) | 2.65 to 3.75 |

Abbreviations: ASDR, age-standardized death rate; EAPC, estimated annual percentage change; GBD, Global Burden of Disease; SDI, sociodemographic index; UI, uncertainty interval.
system leading to omissions in case registers. A global
direct-to-patient cancer medicine donation (Glivec Interna-
tional Patient Assistance Program) provided imatinib to
93 countries, which has improved the survival of patients
with CML. In the future, these countries and regions may
need more health assistance like this.

In addition, it is reported that the mean age of onset was 65
years in 2014-2018. In our study, we found that people
over 70 years old accounted for a larger proportion of all age
groups. This is probably because three mutations in a stem
cell are necessary for chronic disease to develop and
hematopoietic stem cells of older people might have a

![Graph A](image1.png)

**FIG 1.** ASR of incidence and death and change trend of CML in 204 countries or territories in 2019: (A) ASIR, (B) ASDR, (C) EAPC in
ASIR, and (D) EAPC in ASDR. ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASR, age-standardized
rate; CML, chronic myeloid leukemia; EAPC, estimated annual percentage change.

![Graph B](image2.png)

**FIG 2.** Correlation analyses of EAPC-ASR (1990) and EAPC-SDI (2019) in 204 countries or territories: (A) correlation between EAPC of
ASIR and baseline ASIR of 1990, (B) correlation between EAPC of ASDR and baseline ASDR of 1990, (C) correlation between EAPC of
ASIR and SDI of 2019, and (D) correlation between EAPC of ASDR and SDI of 2019. The size of the circle represents the number of
patients with CML in one country or territory. ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASR, age-
standardized rate; CML, chronic myeloid leukemia; EAPC, estimated annual percentage change; SDI, sociodemographic index.
higher rate of t(9;22)(q34; q11) translocation. Age distribution of CML distinguished in different SDI regions. Higher SDI regions had largest proportion of older age, which might have contributed to longer life span. Low SDI regions had the younger incident age and higher death rate, which may be due to worse environment and treatment options. But why young people were more likely to suffer from CML needs to be explored deeper.

The analysis of the relationship between SDI and ASIR/ASDR suggested that when a country develops to a higher extent and has a high economic foundation, its national health can be better guaranteed. Therefore, in these low- and middle-income areas, the leader should give importance to economic development and more medical resources may be needed in the distribution of world health resources. However, several high-income countries like Western Europe, Australasia, and high-income North America with highly aging people had an increased ASIR when the SDI > 0.8. These countries should pay more attention to the prevention and treatment of CML, especially in the elderly.
We summarized four factors causing CML burden, and smoking was a predominant risk factor among these. For CML-related DALYs, about 12,000 males and 40,000 females were due to smoking. Although no detailed biological mechanism has been proposed, several studies suggested a positive correlation between cigarette smoking and CML. 

**FIG 3.** The correlation between CML’s morbidity and mortality and age structure by sex and SDI regions: (A) the correlation between the number or rate of incidence and age groups, (B) the correlation between the number or rate of deaths and age groups, and (C) the correlation between the number or rate of DALYs and age groups. CML, chronic myeloid leukemia; DALYs, disability-adjusted life years; SDI, sociodemographic index.
Globally, tobacco consumption accounts for about 7% and is the second leading cause of the disease burden following high systolic blood pressure. Subgroup analysis of the GBD geographic zone suggested that the ratio of high body mass index accounted for an increasing proportion of all risk factors from 1990 to 2019.
Leptin and adiponectin have been shown to play a role in hematopoietic disorders. Increased cell proliferation, inhibition of apoptosis, impaired immune function, and chronic inflammation were considered the potential mechanism of obesity and CML.\textsuperscript{31,34-36}

Occupational exposure to benzene and occupational exposure to formaldehyde were believed to be related to CML development. There is evidence that occupational handling of benzene is a risk factor and other organic solvents may also be leukemogenic. But the relationship between benzene or formaldehyde and CML needs more evidence. Previously, some situations have reported the CML burden on the basis of GBD 2017. They thought that the CML burden is decreasing or stable, whereas it is increasing according to our analysis.\textsuperscript{37,38} Compared with GBD 2017, GBD 2019 updated cancer mortality data that were added from vital registration system data, verbal autopsy studies, and cancer registry incidence data. The mortality-to-incidence ratio estimation was updated with lower case inclusion criteria and different model hyperparameters, leading to more training data and less smoothing across time and geography. GBD 2019 removed or replaced covariates that had been updated by other GBD teams, assigned a direction of association before all covariates (previously, covariates such as income and sociodemographic index had been allowed to have agnostic direction priors), and changed the minimum age ranges for which the models estimated mortality. These changes made GBD 2019 more representative.

There are also some limitations in our study. First, the main limitation is also the main limitation of GBD database, which is the availability of primary data.\textsuperscript{17} Second, there was substantial regional heterogeneity of the CML data, particularly from low-income and middle-income countries. Third, we only analyzed one database, and if it is possible, adding data from Medline, Embase, Global Health Database, and the WHO library will make the conclusion in this article more accurate. Fourth, the incidence of CML in the last century might have been underestimated because of the backward diagnosis of molecular biology. Fifth, the risk factors reported in this article are global, as no isolated regional or national figures are reported. Getting risk information of region and country may be helpful to policy-makers to take appropriate measures. To summarize, not only will our findings improve understanding of CML determinants and burden worldwide and establish causes of disparities and changes in trends in CML burden between countries of different income levels, but they will also help with the development and monitoring of the effectiveness of CML prevention and management in different countries and populations.

In conclusion, our study comprehensively summarized the temporal trend of CML burden and its attributable factors. Generally, the ASIR, ASDR, and ASR of DALYs decreased sharply in most countries. Although CML seems to be easier to treat, the management of elder patients cannot be neglected. In the past 30 years, the high SDI region made the greatest progress in decreasing CML deaths and DALYs. We predict that low SDI regions will need more health resources and international assistance in the future because of the higher ASIR and highest mortality. Moreover, the role of smoking in DALYs of CML must be paid attention to. High body mass index may become a tricky factor, leading to CML’s DALYs in the future.

**AFFILIATIONS**
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**EQUAL CONTRIBUTION**
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**DATA SHARING STATEMENT**
The data sets generated during and/or analyzed during the current study are available from the Global Health Data Exchange query tool, http://ghdx.healthdata.org/gbd-results-tool.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**
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