National-level dietary patterns and acute myeloid leukemia: a global ecological analysis

In recent years, there has been growing evidence highlighting the important role of dietary factors in the development of hematologic malignancies, particularly acute myeloid leukemia (AML).[1,2] AML is a highly heterogeneous and aggressive hematologic cancer with complex etiologies involving both genetic predispositions and modifiable environmental exposures.[3,4] Emerging studies have suggested that specific dietary components, such as excessive intake of processed meats, refined carbohydrates, and low consumption of protective nutrients, may contribute to leukemogenesis.[5,6] However, most existing studies have been conducted at the individual or cohort level, focusing on personal dietary habits and lifestyle exposures. While informative, these studies are often limited by sample size, recall bias, and lack of global representativeness. Consequently, the dietary determinants of AML on a broader population or country level remain largely unexplored.

To address this gap, we adopted a global ecological perspective by integrating national dietary intake data from the Global Dietary Database (GDD) with AML incidence data from the Global Burden of Disease (GBD 2021) study, enabling evaluation of population-level dietary patterns associated with AML incidence across countries.

Based on biological plausibility, prior literature, and directionally consistent associations with AML risk identified in preliminary analyses, 21 dietary factors were selected from more than 40 components for further analysis. Principal component analysis (PCA) was performed on standardized intake levels to identify underlying dietary structures. The first principal component (PC1), which explained approximately 12% of the total variance and accounted for the largest proportion among the identified dietary patterns, was characterized by high carbohydrate intake and low intake of dairy and protein, with major loadings for cheese, fruit juices, total carbohydrates, total protein, and yoghurt. A generalized linear mixed model (GLMM) was used to estimate associations between dietary patterns and AML incidence, with dietary pattern scores treated as fixed effects and country included as a random intercept, together with age group, sex, socio-demographic index (SDI), and calendar year. The GLMM demonstrated the best model fit based on lower Akaike Information Criterion (AIC) values and improved residual distribution compared with fixed-effects models. Using model-derived relative risks (≈1.02 per 50-point increase in dietary score), we calculated population-attributable fractions (PAF) and estimated the number of AML cases attributable to the dietary pattern in 2018. Negative PAF indicated protective dietary structures, whereas positive PAF reflected increased risk. A Bayesian log-linear model was further applied to project AML burden attributable to this pattern to 2030. All analyses were performed in R version 4.4.1. This study was based exclusively on publicly available, de-identified data from the Global Dietary Database and the Global Burden of Disease (GBD) study and, therefore, did not require approval from a formally constituted ethics review board. All analyses were conducted in accordance with the ethical standards and regulations of the country in which the study was performed.

We first combined data on the intake of 44 dietary components by age group and country from the GDD with age-specific AML incidence data from the GBD database. Using the GLMM framework, we identified dietary factors significantly associated with AML incidence. From these, 21 dietary factors with consistent risk directions were retained for PCA (Figure 1A, *Online Supplementary Table S1*). The resulting PC1 score was significantly and positively associated with AML incidence after adjustment for confounders (Figure 1B). Subgroup analyses showed stronger associations among females and younger-to-middle-aged adults (20-60 years) (Figure 1C, D).

We next quantified the country-specific contribution of this dietary pattern to AML incidence. In 2018, positively attributable cases were rare, whereas negative attributable cases were more frequent, with approximately 600 fewer AML cases in China and 100 fewer in Germany (Figure 2A). Several large-population countries, such as India, exhibited smaller protective effects, indicating potential room for dietary improvement.

The estimated annual percentage change (EAPC) in AML burden attributable to PC1 showed declining trends in countries such as Lebanon and the Philippines, whereas contributions continued to rise in Liberia and Papua New Guinea (Figure 2B, *Online Supplementary Table S2*). Analysis of attributable incidence rates demonstrated substantial between-country heterogeneity, with predominantly negative contributions across most countries and only a few showing positive rates (Figure 3A).

Finally, Bayesian projections indicated persistent global disparities in PC1-attributable AML burden by 2030 (Figure 3B, C, *Online Supplementary Table S3*). China and Germany are expected to continue exhibiting the largest negative contributions, while Ukraine and Japan are projected to show increasing positive contributions. The attributable incidence rate is expected to be highest in Papua New Guinea and lowest in Lebanon.

In this study, we identified a high-carbohydrate, low-dairy, and low-protein dietary pattern that showed a positive as-

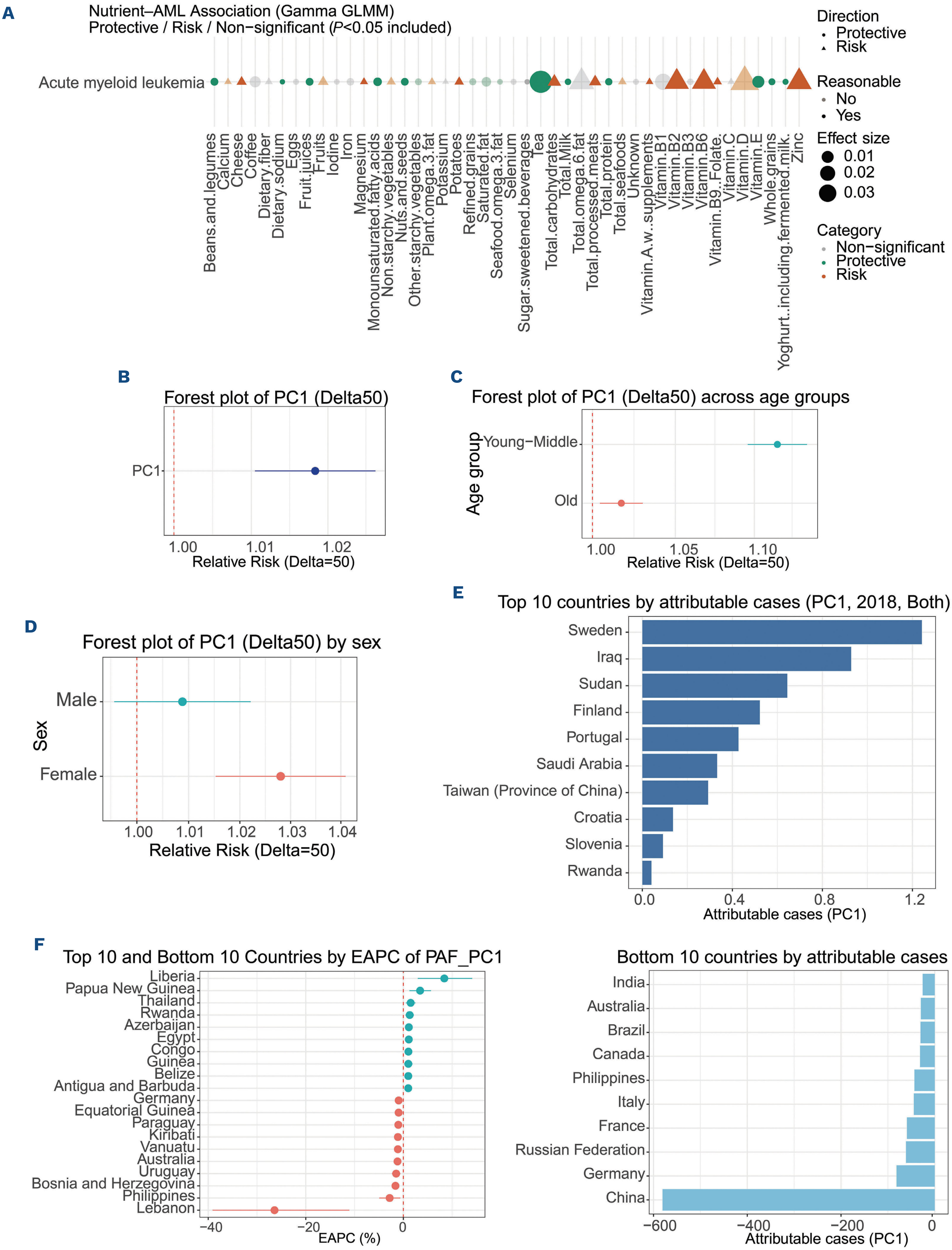

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Figure 1. Global associations between dietary factors, first principal component, and acute myeloid leukemia incidence. (A) A generalized linear mixed model (GLMM) analysis showing the associations of 44 dietary components with the incidence of acute myeloid leukemia (AML) at the national level. (B) GLMM analysis demonstrating the overall association between the first principal component (PC1) and AML incidence after adjustment for age, sex, country, and socio-demographic index (SDI). (C) Association between PC1 and AML incidence stratified by age group (20-60 years *vs.* >60 years). (D) Association between PC1 and AML incidence stratified by sex (male *vs.* female). EAPC: estimated annual percentage change; PAF: population-attributable fractions. (E) Top 10 (upper panel) and bottom 10 (lower panel) countries by attributable AML cases due to PC1 in 2018 (both sexes combined), illustrating positive (risk) and negative (protective) contributions. (F) Top and bottom 10 countries by estimated annual percentage change (EAPC) of PAF_PC1.

sociation with AML incidence at the national level. Although this dietary pattern was overall unfavorable in relation to AML risk, most countries exhibited negative pattern scores, indicating that their prevailing dietary structures were protective rather than harmful. This explains why, despite the risk direction of the pattern, a substantial number of countries experienced reductions in AML cases attributable to this diet. Importantly, the hazard ratio (HR) associated with this dietary pattern was modest, with an estimated HR of approximately 1.02 for every 50-point increase in dietary score. However, because dietary patterns operate at the population level, and national dietary scores often vary by several hundred or even over a thousand points, these small relative risks can translate into large absolute effects on disease burden. For instance, countries such as China and Germany showed the greatest reductions in attributable AML cases, suggesting that even minor shifts in national dietary composition may have considerable public health impact. This between-country heterogeneity likely reflects differences in baseline dietary structures, stages of dietary transition, and population size. However, not all countries have benefited from these protective

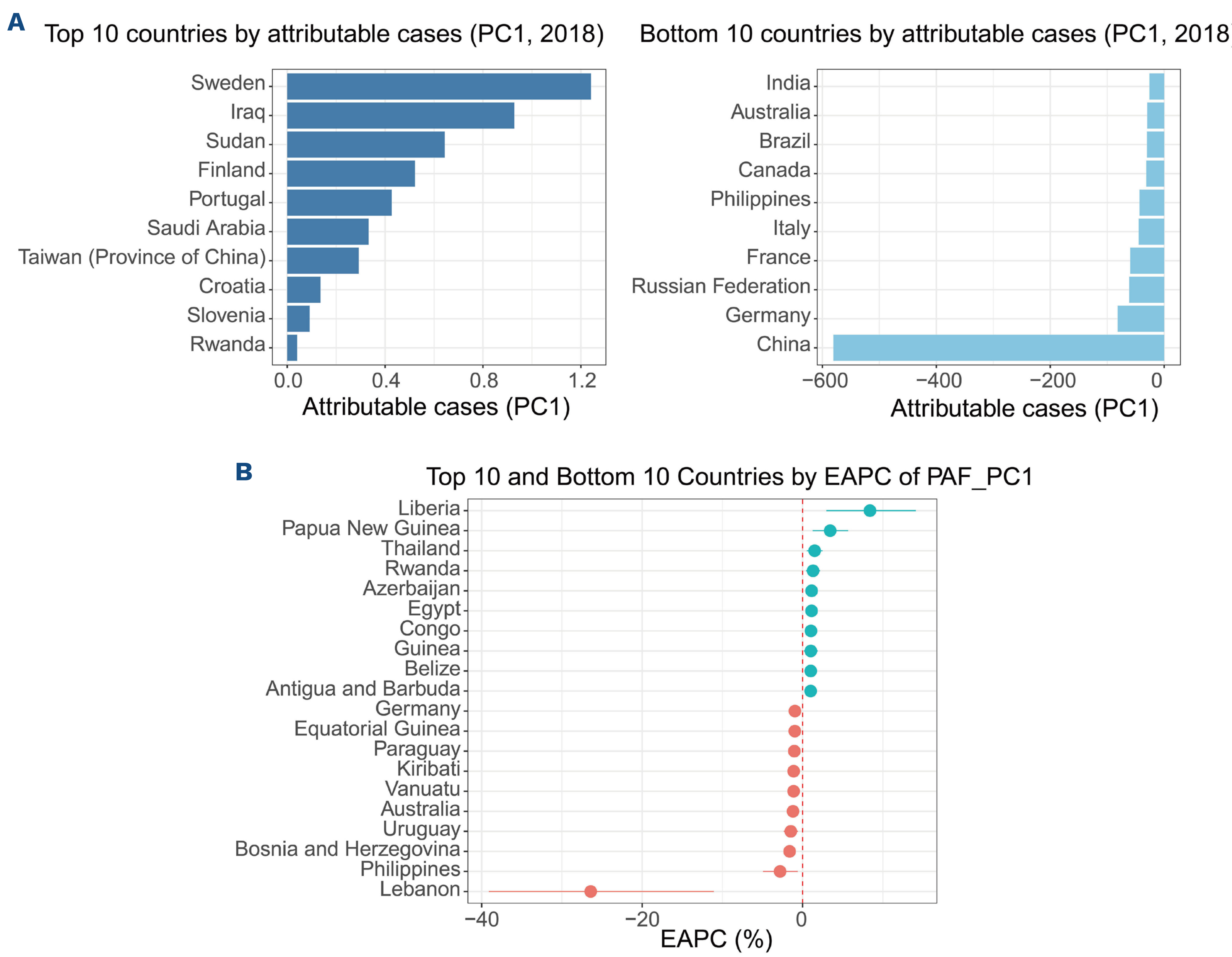

Figure 2. Country-specific acute myeloid leukemia burden attributable to first principal component. (A) Number of acute myeloid leukemia (AML) cases attributable to first principal component (PC1) in 2018 across countries, illustrating both protective (negative) and risk (positive) contributions. (B) The estimated annual percentage change (EAPC) in AML incidence rates attributable to the first principal component (PC1) from 1990 to 2018, reflecting temporal trends in the dietary contribution to AML risk. PAF: population-attributable fractions.

trends. Several nations still exhibit positive dietary pattern scores, implying potential risk increases and emphasizing the global inequality in dietary-related AML burden. From a public health perspective, countries with increasing at-

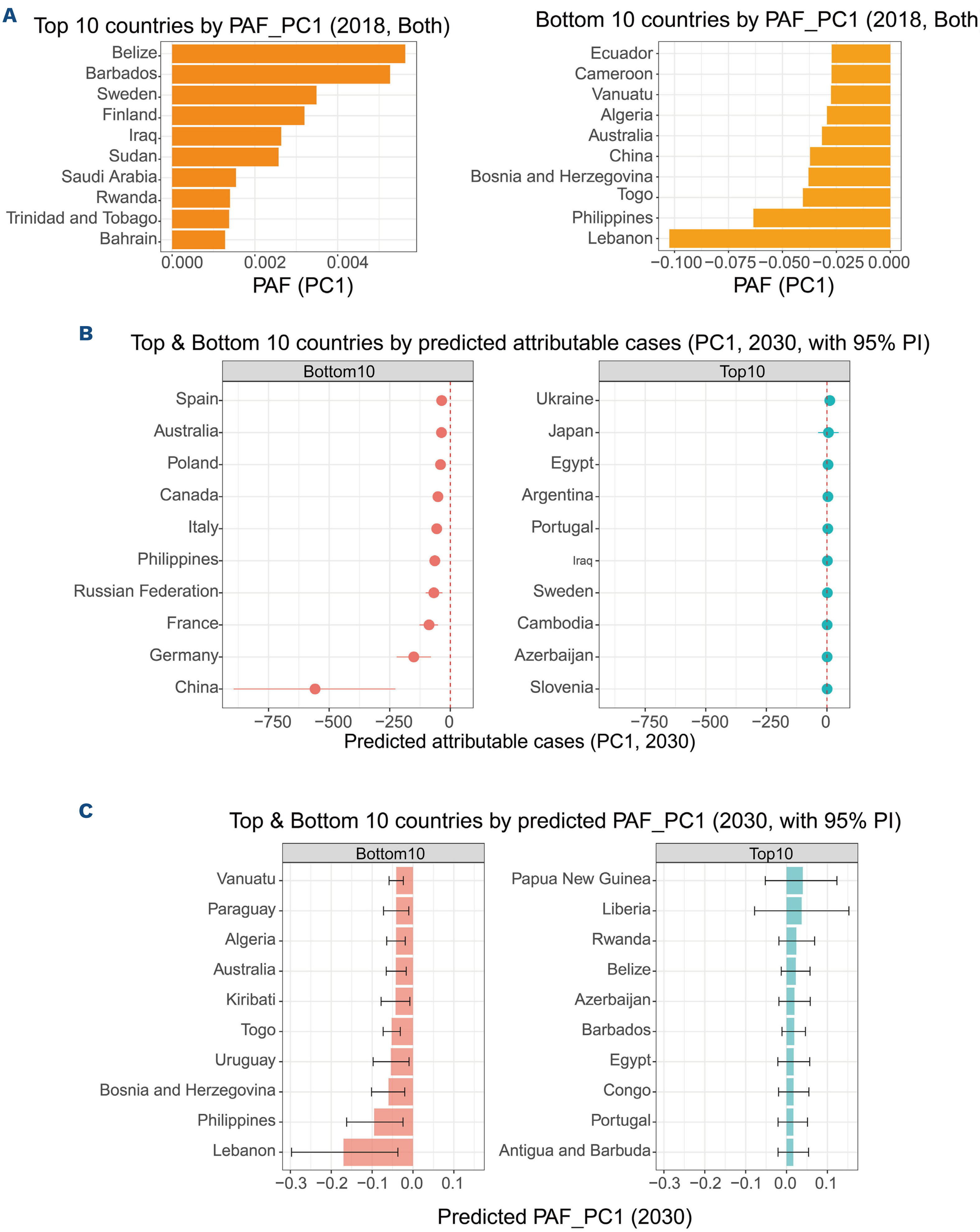

Figure 3. Global distribution and projected acute myeloid leukemia burden attributable to first principal component. (A) Spatial distribution of acute myeloid leukemia (AML) incidence rates attributable to the first principal component (PC1) across countries in 2018. (B) Predicted number of AML cases attributable to PC1 by 2030, based on Bayesian log-linear modeling incorporating country-level random effects. (C) Projected AML incidence rates attributable to PC1 in 2030 for each country, illustrating anticipated shifts in dietary contributions to AML risk. PAF: population-attributable fractions; PI: Prediction Interval.

tributable burden may, therefore, represent priorities for targeted population-level nutritional strategies.

Our subgroup analysis revealed that the association between this dietary pattern and AML incidence was stronger among females and younger-to-middle-aged adults (20-60 years). This may be partially explained by sex-related differences in metabolism, hormonal regulation, and dietary behaviors, which can modify susceptibility to carcinogenic effects of diet.[7] Younger and middle-aged adults may also be more affected because their longer cumulative exposure to modern dietary transitions, characterized by higher carbohydrate intake and lower dairy consumption, interacts with other environmental and occupational risk factors during active working years. At a mechanistic level, high-carbohydrate and low-protein dietary patterns may hypothetically promote leukemogenesis by altering systemic metabolic signaling, including insulin/IGF-1 and downstream mTOR pathways; the responsiveness of these pathways is known to vary by sex hormones and age-related metabolic states, potentially leading to differential effects across population subgroups.[8,9]

It is also noteworthy that while the overall dietary pattern was associated with AML risk, certain individual food components (such as cheese) may independently contribute to either risk or protection, depending on their nutrient content, consumption context, and correlations with other dietary behaviors.[10] Therefore, public health interventions should consider both the aggregate dietary patterns and the effects of specific foods, rather than implementing uniform recommendations.

Finally, this study has some limitations. The GDD contains missing or modeled data for several countries, which may introduce uncertainty into the estimation of national dietary scores. Consequently, while our results provide a comprehensive global overview, individual countries should compute and validate their own dietary pattern scores when designing nutrition-related cancer prevention strategies. In addition, as an ecological analysis, residual confounding from unmeasured factors, such as environmental toxin exposure, healthcare access, and diagnostic capacity, cannot be fully excluded, and some residual confounding related to SDI may persist despite adjustment. Nevertheless, by integrating two authoritative global databases and applying robust analytical methods, our study offers a reliable population-level framework that can inform future mechanistic research and support hypothesis generation for clinical and preventive studies.

Overall, our findings suggest that even modestly risk-associated dietary patterns can exert significant effects at the population level. Evaluating diet at the national level, therefore, provides a practical framework for identifying priority regions and informing population-based nutritional policies, rather than relying solely on individual-level recommendations. In this context, population-level strategies that promote balanced macronutrient intake and healthier national dietary structures may represent a feasible complement to existing AML prevention efforts.

Integrating national dietary surveillance with AML prevention efforts could help further reduce leukemia burden worldwide, particularly in regions that have not yet benefited from the prevailing protective dietary trends. Future research should integrate molecular mechanistic investigations with analyses in more finely stratified populations to clarify causal pathways and identify vulnerable subgroups.

Authors

Diguang Wen,[1] Zhenxiang Peng[2] and Jianchuan Deng[1]

[1]Department of Hematology and [2]Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

Correspondence:
J. DENG - dengjianchuan66@163.com
300319@hospital.cqmu.edu.cn

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Contributions

JD designed the study; DW performed the data analysis and drafted the manuscript; ZP prepared the tables and figures. All authors reviewed and approved the final version of the manuscript for publication.

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Data-sharing statement

The data used in this study are publicly available from the Global Dietary Database (GDD) 2018 and the Global Burden of Disease (GBD) 2021 databases.

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