

Combined Neurodevelopmental and Neurodegenerative Burden: Lifetime DALYs from Pesticide Exposure in MENA Agricultural Communities

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Abstract

Pesticide exposure in agricultural populations poses well-documented neurotoxic risks, yet comprehensive burden of disease assessments remain absent for the Middle East and North Africa (MENA) region—home to 450 million people with intensive agricultural practices. We quantified lifetime disability-adjusted life years (DALYs) attributable to pesticide-induced neurological disorders across 18 MENA countries from 2010-2023, focusing on prenatal neurodevelopmental impacts (intellectual disability from IQ decrements) and adult neurodegenerative disease (Parkinson's disease). Country-specific exposure prevalence was estimated from agricultural employment patterns (occupational pathway) and rural population distributions (environmental pathway), with pesticide application intensity derived from FAO statistics. We applied exposure-response coefficients from prospective birth cohort studies for neurodevelopment and meta-analytic relative risks for Parkinson's disease, calculating population attributable fractions and age-specific burden using Global Burden of Disease methodology. Regional burden reached 568,329 DALYs annually, with Egypt, Yemen, and Algeria accounting for 61% of total impact despite representing 32% of population. Neurodevelopmental burden dominated (90% of DALYs), challenging conventional adult-focused occupational health paradigms. Per-capita burden rates (229-235 DALYs per 100,000 in highest-burden countries) reached magnitudes comparable to lead exposure in contaminated populations, yet receive substantially less policy attention. An apparent inverse relationship

between pesticide intensity and Parkinson's disease burden ($\rho=-0.35$, $p=0.14$) was explained by agricultural mechanization confounding rather than causal dose-response: Gulf countries have high pesticide intensity (capital-intensive greenhouse systems) but minimal PD burden (young, urbanized populations with low baseline PD rates). Excluding these outlier countries eliminated the inverse relationship ($\rho=+0.28$, $p=0.36$), though the positive association remained non-significant. These findings establish pesticide neurotoxicity as a major environmental health determinant in MENA, with prenatal and early-life exposure representing critical intervention windows requiring hazard-based chemical restrictions, spatial buffer zones, and occupational health programs targeting aging farmworker populations.

Keywords

Pesticides; Neurodevelopmental disorders; Parkinson's disease; Disability-adjusted life years; Intellectual disability; Population attributable fraction; Middle East; North Africa; Global burden of disease

Introduction

Pesticide use has become integral to modern agriculture, with global consumption exceeding 3.5 million tonnes annually to meet the food demands of a growing population [1]. Mounting evidence suggests that widespread pesticide exposure carries substantial public health consequences that extend beyond acute toxicity [2-4]. The Middle East and North Africa (MENA) region, characterized by intensive agricultural practices and relatively high pesticide application rates, faces particular vulnerability to these health impacts [5]. Despite this concern, comprehensive assessments of the population-level health burden attributable to pesticide exposure in MENA countries remain notably absent from the scientific literature.

Two distinct but interconnected pathways link pesticide exposure to long-term neurological harm across the human lifespan. Prenatal and early-life exposure to organophosphate pesticides has been consistently associated with neurodevelopmental deficits in children, including decreased intelligence quotient (IQ) scores, attention problems, and increased prevalence of intellectual disability (ID) [6-9]. These effects occur through mechanisms that may be independent of acetylcholinesterase inhibition, the classical pathway of organophosphate toxicity, and appear to manifest even at exposure levels previously considered safe [10]. Separately, chronic occupational and environmental pesticide exposure in adulthood has been linked to increased risk of neurodegenerative diseases, particularly Parkinson's disease (PD), with meta-analyses reporting relative risks ranging from 1.6 to 2.0 for occupationally exposed populations [11, 12]. The convergence of these two pathways suggests that populations in agricultural regions experience a cumulative neurological burden that begins in utero and extends throughout the lifespan. While these pathways operate through distinct biological mechanisms at different life stages, they represent complementary manifestations of pesticide neurotoxicity across the life course. This approach follows Global Burden of Disease methodology, which routinely aggregates multiple health outcomes attributable to single environmental exposures to quantify total population health impact [13].

The Global Burden of Disease (GBD) study framework provides standardized methods for quantifying population health impacts using disability-adjusted life years (DALYs), a composite metric that combines years of life lost due to premature mortality and years lived with disability [13]. Existing burden of disease estimates for neurodevelopmental impacts of environmental toxicants have primarily focused on lead exposure [14, 15], with pesticides receiving comparatively less quantitative assessment despite growing epidemiological evidence of harm. Furthermore, previous studies typically focused on acute poisoning rather than the full spectrum of chronic neurological effects across the lifespan [16].

Countries in MENA region, including Egypt, Morocco, Algeria, Tunisia, Jordan, Lebanon, and others, maintain substantial agricultural sectors that employ significant proportions of their populations and utilize pesticides at rates that often exceed global medians [17]. Simultaneously, these countries face challenges in occupational health regulation, pesticide stewardship, and public health surveillance that may amplify population exposure risks [18]. The sociodemographic characteristics of MENA populations, including high birth rates and substantial rural populations living in proximity to agricultural areas, further elevate the potential for widespread exposure and consequent health impacts [17]. Despite these risk factors, no previous study has systematically quantified the combined neurodevelopmental and neurodegenerative burden attributable to pesticide exposure across MENA countries using standardized burden of disease methodology.

This study addresses these gaps by providing the first comprehensive assessment of lifetime DALYs attributable to pesticide exposure in MENA agricultural communities, integrating both childhood neurodevelopmental impacts and adult neurodegenerative disease (Parkinson's disease). Our approach is novel in three key respects. First, we combine estimates of ID arising from prenatal pesticide-induced IQ decrements with estimates of PD attributable to occupational and environmental exposure, providing a lifespan perspective on pesticide neurotoxicity that has not been previously quantified at the population level. Second, we employ country-specific exposure assessments based on agricultural employment patterns, pesticide application intensity, and rural population distributions rather than uniform regional assumptions, allowing burden estimates to reflect local conditions and enabling cross-country comparisons that can identify high-priority settings for intervention. Third, we link ecological exposure indicators (regional pesticide application rates) to individual-level health outcomes using exposure-response coefficients from prospective epidemiological studies, demonstrating a pragmatic modeling approach applicable to regions where individual exposure biomarker data are unavailable. Our specific objectives are to estimate the annual burden of ID attributable to prenatal pesticide exposure across MENA countries expressed as years lived with disability; to quantify the burden of PD attributable to occupational and environmental pesticide exposure expressed as attributable mortality, years of life lost, and years lived with disability; and to characterize how the combined lifetime neurological burden varies across countries with different agricultural intensities. Through these analyses, we aim to provide evidence that can inform pesticide regulation policies, occupational health interventions, and public health resource allocation in a region where such data have been critically lacking.

Methods

We conducted a comparative risk assessment to estimate the neurological health burden attributable to pesticide exposure in Middle East and North Africa (MENA) countries for the years 2010 through 2023. Our analysis integrated two distinct causal pathways: prenatal exposure leading to neurodevelopmental deficits manifesting as intellectual disability (ID) (ICD-10: F70-F79) in children, and chronic occupational and environmental exposure leading to PD (ICD-10: G20) in adults. We followed established methods for environmental burden of disease assessment [19] and adapted the population attributable fraction (PAFs) approach used in Global Burden of Disease (GBD) studies [13]. All analyses were conducted between January 2024 and January 2026 using Microsoft Excel version 16.0.

Study Population and Geographic Scope

We included all countries in the Middle East and North Africa region for which complete data on pesticide use, agricultural employment, population demographics, and baseline disease burden were available. The final analysis included Egypt, Morocco, Algeria, Tunisia, Libya, Sudan, Lebanon, Jordan, Syria, Iraq, Yemen, Palestine, Saudi Arabia, United Arab Emirates, Kuwait, Oman, Bahrain, and Qatar, as well as global aggregate estimates for comparative context, representing diverse agricultural practices ranging from intensive irrigated farming to pastoral systems across approximately 450 million people in the MENA region. We defined the exposure period as prenatal exposure for neurodevelopmental outcomes (occurring during the nine months of gestation in each year from 2010 to 2023) and cumulative lifetime exposure for PD outcomes (with disease manifestation in each year following decades of exposure).

Data Sources

We obtained country-specific pesticide use data from the Food and Agriculture Organization Corporate Statistical Database (FAOSTAT), which provides annual reports of total pesticide consumption in tonnes and agricultural land area in hectares for each country [17]. We extracted annual data on pesticides used in agriculture from 2010 through 2023. For countries with incomplete annual reporting, we used available data from the nearest years and carried forward the most recent value for years with missing data, acknowledging that this approach may not capture recent changes in pesticide use patterns. We calculated pesticide application intensity as kilograms of active ingredient per hectare of agricultural land for each country. We obtained population data, including total population size, and annual births, from the United Nations World Population Prospects 2024 revision [20], extracting annual estimates for each year from 2010 through 2023. For rural population estimates, we relied on the World Bank Database [21]. We extracted country-specific agricultural employment data from the database of Our World Data [22], which reports the number and proportion of workers employed in the agricultural sector. For years 2020 through 2023, where agricultural employment data were unavailable due to reporting lags, we carried forward the 2019 values, assuming stable agricultural workforce proportions in the absence of updated data.

We obtained baseline PD burden data from the GBD Study 2023, accessed through the Institute for Health Metrics and Evaluation data visualization tool [23]. For each country, we extracted the number of deaths, disability-adjusted life years (DALYs), years of life lost (YLL), years lived with disability (YLD), and prevalence of PD for both sexes combined, all ages, for the years

2010 through 2023. The uncertainty intervals were not consistently available across all countries and years in the GBD 2023 dataset. Therefore, we used the mean estimates rather than uncertainty intervals for the primary analysis. Instead of bootstrapping, which would require unverifiable distributional assumptions, we conducted deterministic sensitivity analyses varying all key parameters across their epidemiologically plausible ranges.

Exposure Assessment

We developed country-specific estimates of exposure prevalence for both occupational and environmental pathways. For countries where pesticide intensity fell below the reference threshold (0.1 kg/ha), the intensity ratio was less than 1.0, which would mathematically imply a protective intelligence quotient (IQ) effect inconsistent with toxicological evidence. In these cases (Iraq during 8 of 14 study years: 2013-2020), excess ID prevalence was censored to zero for those specific years, yielding attributable burden from PD only during the censored period. Iraq's mean burden estimates in Table 1 represent averages across all 14 years (2010-2023), including both censored years (PD-only burden) and uncensored years (combined ID and PD burden).

Occupational exposure prevalence was calculated by multiplying the agricultural population proportion by an exposure fraction of 0.80, a value derived from biomonitoring studies showing 70–85% of farmworkers have detectable pesticide metabolites [24, 25]. Environmental exposure was estimated by applying a baseline proximity fraction of 0.58—representing homes within a 500m drift zone [26]—to the total rural population. Although the rural population includes agricultural workers, the application of a country-specific pesticide intensity modifier (kg/ha) relative to a 0.1 kg/ha threshold ensures that combined exposure prevalence remains biologically plausible and below 100% across all country-years. This modifier, capped at 10-fold, accounts for elevated risks from drift, water contamination, and household use in high-intensity regions [27, 28], aligning with Global Burden of Disease risk-weighting [13] and Comparative Risk Assessment frameworks [19].

We validated these exposure prevalence assumptions against published biomonitoring studies from agricultural communities worldwide (Supplementary Figure 1). Analysis of 18 estimates from 15 studies spanning 2000-2023 revealed weighted mean detection rates of organophosphate metabolites of 83.9% among occupationally exposed populations [29-32] and 85.1% among environmentally exposed populations including rural residents, pregnant women in agricultural areas, and children in farmworker households [28, 33-42]. These empirical findings support our model assumptions of 80% occupational and 58% environmental exposure prevalence.

Neurodevelopmental Burden Estimation

We estimated the burden of ID attributable to prenatal pesticide exposure using an IQ distribution shift methodology consistent with established approaches for quantifying population-level impacts of neurodevelopmental toxicants [14, 15, 43]. We assumed that IQ is normally distributed in the population with a mean of 100 and standard deviation of 15, consistent with standard psychometric theory. Under this assumption, 2.28 percent of the

population has an IQ below 70 [44], the diagnostic threshold for ID, calculated as the cumulative probability of a standard normal distribution at -2.0 standard deviations from the mean.

We applied IQ shift coefficients derived from Bouchard et al. (2011), who reported a 5.6-point decrease in full-scale IQ (95 percent confidence interval: 2.2 to 9.0) per 10-fold increase in maternal urinary organophosphate metabolite concentrations during pregnancy in the CHAMACOS prospective birth cohort study [6]. We converted this coefficient to a natural logarithm scale by dividing by 2.303 (the natural logarithm of 10), yielding a coefficient of -2.43 IQ points per natural log unit increase in exposure. We calculated IQ shifts for each country by multiplying the pesticide intensity ratio by the coefficient of -2.43. To avoid implausible extrapolation beyond the CHAMACOS cohort's observed exposure range, we capped IQ decrements at 9.0 points, corresponding to the upper 95% confidence interval from Bouchard study [6]. This cap was applied to all country-years where calculated decrements exceeded 9.0 points, affecting 9 countries (Kuwait, Qatar, Palestine, Bahrain, Lebanon, United Arab Emirates, Oman, Egypt, Jordan) across 63 country-years (24% of observations), predominantly in Gulf states with intensive greenhouse agriculture systems where pesticide application rates exceeded 1,000-fold the reference threshold.

We used country-specific pesticide application intensity as a proxy for population-level prenatal exposure, calculating exposure ratios relative to a reference level of 0.1 kilograms per hectare to allow interpretation of IQ shifts as incremental effects of increasing pesticide exposure above baseline agricultural practice. The 0.1 kg/ha reference threshold based on several considerations. First, it represents truly minimal use scenarios [45]. Second, this threshold ensures that the exposure-response relationship derived from Bouchard et al. [6] is applied appropriately: their study quantified IQ decrements associated with increased organophosphate exposure relative to lower-exposed comparison groups. Third, this ensures that countries with low pesticide intensity are not incorrectly assigned negative neurological health burdens, which would be inconsistent with the toxicological evidence showing a monotonic dose-response relationship between organophosphate exposure and neurodevelopmental harm [46]. For countries where pesticide application intensity fell below the reference threshold, the calculated intensity ratio was less than 1.0, yielding mathematically positive IQ shifts that would imply protective neurodevelopmental effects. As this is inconsistent with established organophosphate neurotoxicity, we censored excess ID prevalence to zero in these instances. This censoring applied to Iraq for 8 of 14 study years (2013-2020), during which pesticide intensity ranged from 0.030 to 0.094 kg/ha. For these years, Iraq's attributable burden reflects PD contribution only.

For each country, we calculated the proportion of the population falling below the ID threshold after the pesticide-induced IQ shift by evaluating the normal cumulative distribution function at an IQ of 70 with the shifted mean. We subtracted the baseline prevalence of 2.28 percent to obtain the excess prevalence attributable to pesticide exposure [44]. We multiplied this excess prevalence by the annual number of births in each country to estimate the number of children born annually with pesticide-attributable ID. This approach captures both clinically diagnosed ID and undiagnosed cases of cognitive impairment, representing the full biological impact of pesticide-induced IQ decrements on population neurodevelopment.

We translated ID cases into years lived with disability by applying disability weights from the Global Burden of Disease Study 2023 [13]. The GBD 2023 provides severity-specific disability weights for ID: mild (0.043), moderate (0.10), and severe (0.16). We calculated a weighted average disability weight of 0.058 by applying these GBD weights to the typical severity distribution among individuals with IQ below 70 points: 85% mild, 10% moderate, and 5% severe [47]. This calculation yields: $(0.85 \times 0.043) + (0.10 \times 0.10) + (0.05 \times 0.16) = 0.058$. We multiplied the number of attributable cases by the discounted lifetime years lived with disability per case to obtain total annual neurodevelopmental years lived with disability for each country.

Neurodegenerative Burden Estimation

We estimated the burden of PD attributable to pesticide exposure using the population attributable fractions (PAFs) methodology [13, 48]. The PAFs represent the proportion of disease in a population that would be eliminated if the exposure were removed, assuming a causal relationship. We calculated PAFs for occupational and environmental exposure pathways using the standard formula: $PAF = [P \times (RR - 1)] / [1 + P \times (RR - 1)]$, where P is exposure prevalence and RR is relative risk [48]. We obtained RR estimates of pesticide exposure and PD. For occupational exposure, we used a RR of 1.5 (95% CI: 1.3 to 1.7) from published meta-analyses [11, 12, 49, 50], which pooled case-control and cohort studies examining occupational pesticide exposure among farmworkers and pesticide applicators. For environmental exposure, we used a RR of 1.25 based on studies of residential proximity to agricultural pesticide applications [51-53]. We calculated separate PAFs for occupational and environmental pathways using the country-specific exposure prevalence estimates described earlier, then combined these fractions using the formula for independent competing exposures:

$PAF_{combined} = 1 - [(1 - PAF_{occ}) \times (1 - PAF_{env})]$. The combined PAF formula was applied to the entire population, accounting for: (1) non-agricultural rural residents exposed only environmentally (PAF_{env}), (2) agricultural workers in urban/peri-urban areas exposed only occupationally (PAF_{occ}), and (3) rural agricultural workers with both exposures. The multiplicative formula prevents double-counting attributable cases in the overlap group.

We multiplied the combined PAFs for each country by the baseline PD burden obtained to estimate attributable mortalities, DALYs, YLL, and YLD. This approach assumes that the RR from predominantly Western populations apply to MENA populations and that the causal relationship between pesticide exposure and PD is consistent across different exposure intensities within the range observed in our study countries.

For PD, we used an age-weighted disability weight of 0.371, calculated as the population-weighted average of GBD 2023 severity-specific PD disability weights (mild: 0.256, moderate: 0.408, severe: 0.548) applied to the MENA PD severity distribution, with moderate-severity cases constituting 76% of prevalent cases based on the region's younger PD patient age structure compared to high-income countries [13]. We calculated the present value of lifetime years lived with disability for each case by summing discounted years over a 72-year lifespan (the average life expectancy in MENA countries) [54] using a 4.5 percent annual discount rate [55], consistent with recent economic evaluations of health interventions [56]. The annual discount rate reflects standard economic principles that society values health improvements in the present more than equivalent improvements in the distant future, consistent with WHO guidelines [57].

Combined Lifetime Burden

We calculated total lifetime DALYs attributable to pesticide exposure by summing the neurodevelopmental YLD and the neurodegenerative DALYs (which include both YLL and YLD from PD). We expressed results as absolute numbers of DALYs and as rates per 100,000 population to facilitate comparison across countries with different population sizes. We calculated the relative contribution of neurodevelopmental versus neurodegenerative burden for each country to characterize the age distribution of pesticide-attributable health impacts.

Sensitivity Analyses

We conducted comprehensive sensitivity analyses to assess the robustness of our estimates to uncertainties in key parameters. We varied the RR for occupational PD between 1.3 (lower 95% CI bound) and 1.7 (upper bound), the IQ shift coefficient between -0.96 and -3.91 (the 95 % CI from Bouchard et al. [6]), and the exposure prevalence assumptions between 60 percent and 90 percent for occupational exposure and between 20 percent and 45 percent for environmental exposure. For each sensitivity scenario, we recalculated the full burden estimate and determined the minimum and maximum estimates across all scenarios to establish uncertainty intervals. Epidemiological parameters, data sources, and their relative contributions to model uncertainty are summarized in Table 2. We present these intervals alongside our primary estimates to characterize the range of plausible burden estimates given current epidemiological evidence.

Table 2. Epidemiological Parameters, Assumptions, and Sensitivity Analysis

Parameter	Base_Case_Value	Sensitivity_Range	Source_Refere nce	Contribution_to_U ncertainty_Percent
Relative Risk (PD, Occupational)	1.5	1.30, 1.70	[49, 50]	-0.30%
Relative Risk (PD, Environmental)	1.25	1.15, 1.35	[51, 58]	
IQ Shift Coefficient (Beta)	-2.43 IQ points per ln unit	-0.96 to -3.91 (capped at -9.0 IQ points)	[6]	171.40%
Occupational Exposure Prevalence	80% of agricultural workers	60, 90%	[59], <i>Supplementary Figure 1</i>	1.30%
Environmental Exposure Prevalence	58% of rural residents intensity modifier	40, 75%	[26], <i>Supplementary Figure 1</i>	1.30%
PD Disability Weight (weighted average)	0.371 (age-weighted)	Fixed	[23]	
ID Disability Weight (weighted average)	0.058 (severity-weighted)	Fixed	[47, 60]	
Discount Rate	4.5% per year	Fixed (sensitivity: 0%, 3%, 4.5%)	[55]	
Life Expectancy (MENA average)	72 years	Fixed	[21]	

Notes: Base case values represent central estimates used in primary analysis. Sensitivity ranges indicate parameter variations tested in uncertainty quantification. Contribution to total uncertainty calculated as percentage of total burden variance attributable to each parameter

when varied from base to extreme values across all countries and years. IQ Shift Coefficient capped at -9.0 IQ points ([6], upper 95% CI) to avoid implausible extrapolation beyond observed exposure range. Negative uncertainty contribution for RR (PD, Occupational) indicates inverse relationship between parameter value and aggregate uncertainty due to model structure.

Age-Standardized Burden Rate Calculations

Age-standardized burden rates were calculated to enable valid comparisons between MENA and global populations with different age structures, following WHO methods for direct standardization. We first distributed country-specific pesticide-attributable DALYs across 16 five-year age groups (0-4, 5-9, ..., 70-74, 75+) using age-specific prevalence patterns from the GBD Study 2023. For each country and year, the proportion of total PD cases in age group i was calculated as the number of PD cases in that age group divided by the sum of PD cases across all age groups; this proportion was then multiplied by the total pesticide-attributable PD DALYs to obtain age-specific PD burden. The same procedure was applied to ID burden. Age-specific burden rates (per 100,000 population) were calculated by dividing age-specific DALYs by age-specific population estimates from UN World Population Prospects 2024. Age-standardized rates were then computed using the WHO World Standard Population as the reference, calculated as: $ASR = \sum(r_i \times w_i) / \sum(w_i)$, where r_i is the age-specific rate in age group i and w_i is the WHO standard population weight for that age group. This standardization removes the confounding effect of different age structures, enabling unbiased comparisons of pesticide-attributable neurological burden between MENA countries and global populations. The WHO World Standard Population assigns higher weights to younger age groups (e.g., 8,800 per 100,000 for ages 0-4) and lower weights to elderly groups (e.g., 2,200 per 100,000 for ages 75+), representing an average global age distribution. Age-standardized rates were compared to crude (unadjusted) rates to quantify the degree of demographic confounding, with ratios >1 indicating that crude rates underestimate true population risk due to younger-than-standard age structures.

Statistical Analysis

We performed all calculations using Microsoft Excel version 16.0. We used standard normal distribution functions for IQ shift calculations, applied PAFs formulas for PD burden estimation, and calculated present values using standard discounting equations. Paired t-tests (two-sided, $\alpha = 0.05$) were used to compare mean annual burden rates between each MENA subregion and global rates across the 14-year study period (2010–2023), treating annual observations as paired measurements. All data sources were publicly available and did not require ethical review or informed consent.

Figures were produced in RStudio (2025.09.2+418, Cucumberleaf Sunflower) using tidyverse and ggplot2 for data handling and plotting, corrplot for correlation matrices, sf / rnatualearth for maps, and cowplot/ggpubr for arranging panels. Data tables exported from the analysis workbook were read with readxl and cleaned with dplyr. Maps used Natural Earth geometry joined to country-level summary tables. Country comparison plots used summary statistics aggregated across 2010–2023. Absolute burden panels displayed mean annual DALYs with 95% confidence intervals computed from the annual standard deviation ($n = 14$ years). Per-capita

panels used rates per 100,000. Subregions were defined a priori: “North Africa” (Egypt, Morocco, Algeria, Tunisia, Libya, Sudan), “Levant” (Lebanon, Jordan, Syria, Palestine), “Gulf” (Saudi Arabia, United Arab Emirates, Kuwait, Oman, Bahrain, Qatar), and “Other” (Iraq, Yemen).

Results

Regional Pesticide Exposure Landscape

Pesticide application intensity across the MENA region exhibited non-monotonic temporal patterns from 2010 to 2023, rising from 0.91 kg/ha in 2010 to a peak of 1.08 kg/ha in 2019 before declining to 0.95 kg/ha by 2023 (Figure 1A). Agricultural employment declined progressively from 6.97% to 4.92% of the workforce, while rural population decreased from 43.5% to 40.2% over the same period. Country-specific pesticide intensity trajectories revealed marked heterogeneity (Figure 1B): Kuwait demonstrated the highest mean intensity (175.4 kg/ha) with pronounced volatility (range: 119.8-264.2 kg/ha), peaking at 264.2 kg/ha in 2015 before declining to 147.6 kg/ha in 2023. Qatar exhibited a 75% reduction from 207.8 kg/ha (2010) to 51.9 kg/ha (2023), while Palestine (mean 27.2 kg/ha) and Lebanon (13.7 kg/ha) maintained relatively stable application rates throughout the study period.

-----Insert Figure 1 here -----

Estimated exposure prevalence varied substantially across countries (Figure 2). Morocco demonstrated the highest combined exposure (12.0% of population: 9.8% occupational, 2.3% environmental), followed by Sudan (9.5%: 8.8% occupational, 0.6% environmental), Egypt (9.0%: 5.7% occupational, 3.3% environmental), and Yemen (7.4%: 4.2% occupational, 3.3% environmental). Environmental exposure contributed most substantially in Yemen (44.0% of combined exposure) and Egypt (37.0%), while occupational exposure overwhelmingly dominated in Morocco (81.1%), Sudan (93.1%), and Libya (89.6%). Gulf countries exhibited minimal exposure prevalence: Bahrain (0.5%, entirely occupational), Kuwait (0.9%), and Qatar (0.9%), reflecting near-complete urbanization (>95% of population) despite intensive greenhouse operations [61].

-----Insert Figure 2 here -----

Geographic Distribution of Neurological Burden

Total pesticide-attributable neurological burden across 18 MENA countries reached a mean of 568,329 DALYs annually (2010-2023), affecting an estimated 450 million people (Figure 3, Figure 4). Egypt bore the highest absolute burden (203,275 DALYs annually: 182,588 intellectual disability (ID) YLDs + 20,687 PD DALYs), representing 35.8% of the regional total, followed by Yemen (77,615 DALYs: 74,495 ID + 3,121 PD) and Algeria (65,223 DALYs: 58,273 ID + 6,951 PD). Neurodevelopmental burden constituted 81.1% to 99.9% of total DALYs across 17 countries. Iraq, where ID burden was censored to zero during 8 of 14 study years (2013-2020) when pesticide intensity fell below the 0.1 kg/ha reference threshold, showed reduced neurodevelopmental contribution (69.4% averaged across all years) due to averaging

across mixed censored and uncensored periods. Iraq is included in all regional totals and the 18-country count.

-----Insert Figure 3 here -----

Per-capita burden rates revealed different country rankings (Figure 3B). Yemen exhibited the highest rate (234.6 DALYs per 100,000 population; 95% CI: 213-256), followed by Palestine (228.9 per 100,000; 95% CI: 219-239) and Egypt (200.1 per 100,000; 95% CI: 189-211). Egypt's large population generated the highest absolute burden while maintaining a notably high per-capita rate, the third highest in the region.

-----Insert Figure 4 here -----

Multidimensional country risk profiles across four dimensions—pesticide intensity, per-capita burden rate, population attributable fraction, and temporal change—revealed distinct patterns among top burden countries (Figure 5). Egypt exhibited maximal pesticide intensity (3.9 kg/ha) and PAF (46.9%) with high per-capita rate (200.1 per 100,000) but minimal temporal change (+5.7% from 2010-2023). Yemen demonstrated the highest temporal increase (+132.2%), maximal per-capita rate (234.6 per 100,000), and near-maximal PAF (45.6%) despite low pesticide intensity (0.99 kg/ha). Algeria showed the largest temporal increase (+219.4%)—nearly tripling burden over 14 years—despite modest intensity (0.81 kg/ha) and moderate per-capita rates (158.5 per 100,000).

-----Insert Figure 5 here -----

Neurodevelopmental Burden: Intellectual Disability

Pesticide intensity demonstrated a strong positive association with ID burden across countries (Figure 6A; Spearman $\rho = 0.87$, $p < 0.001$). Yemen (225.2 YLDs per 100,000 at 0.99 kg/ha) and Palestine (223.0 YLDs per 100,000 at 27.2 kg/ha) exhibited the highest burden rates despite 27-fold difference in application intensities. The regression slope of 37.4 YLDs per 100,000 per $\log_{10}(\text{kg/ha})$ indicated that each 10-fold pesticide intensity increase corresponded to an average 37.4 YLD per 100,000 burden increase.

Country-specific mean intelligence quotient (IQ) decrements ranged from 1.62 points in Iraq (95% CI: 0.89-2.36) to 9.0 points (capped) in ten countries (Figure 6B). The 9.0-point biological plausibility cap was applied to Kuwait, Qatar, Palestine, Bahrain, Lebanon, UAE, Oman, Egypt, Jordan, and Morocco—ten countries representing 55.6% of MENA countries—where pesticide intensities exceeded 70-1,750 fold above the 0.1 kg/ha reference threshold. Five additional countries experienced partial capping in some years: Saudi Arabia (13 of 14 years), Tunisia (11 years), Yemen (7 years), Libya (2 years), and Algeria (3 years). Uncapped countries demonstrated graded decrements: Iraq (1.62 points), Sudan (1.93), Syria (5.48), Algeria (7.88), Libya (8.10), Yemen (8.26), Tunisia (8.81), and Saudi Arabia (8.98).

-----Insert Figure 6 here -----

Pesticide exposure accounted for substantial proportions of total ID burden across MENA countries (Figure 7). Ten countries with consistently capped IQ decrements—Bahrain, Egypt, Jordan, Kuwait, Lebanon, Morocco, Oman, Palestine, Qatar, and UAE—each individually exhibited ID PAF of 71.8% (unweighted mean across countries). However, when weighted by population size to calculate the regional aggregate, MENA's ID PAF was 65.8%, reflecting the influence of larger countries (Egypt, Saudi Arabia) with lower individual PAFs. Three additional countries with partial capping showed high PAFs: Saudi Arabia (71.7%), Tunisia (71.1%), and Yemen (69.2%). Countries with predominantly uncapped IQ decrements showed lower PAFs: Iraq (13.8%; mean 2,369 YLDs/year), Sudan (26.1%; 15,311 YLDs/year), Syria (55.3%; 16,922 YLDs/year), Algeria (67.8%; 58,273 YLDs/year), and Libya (68.6%; 8,539 YLDs/year). At the regional aggregate level, MENA generated 513,349 pesticide-attributable ID YLDs annually (95% CI: 499,697-527,002), representing 65.8% of total ID burden. The MENA per-capita attributable rate (128.2 YLDs per 100,000) was lower than the global rate (133.1 per 100,000) despite similar PAFs.

-----Insert Figure 7 here -----

Neurodegenerative Burden: Parkinson's Disease (PD)

Population attributable fractions for PD varied substantially across countries, ranging from <1% in Gulf countries to 47% in Egypt (Figure 8). Egypt demonstrated the highest combined PAF (46.9%; 95% CI: 46.8-47.0), followed by Yemen (45.6%; 42.6-48.6) and Morocco (39.1%; 38.6-39.7). Mid-range PAFs were observed in Algeria (25.4%), Tunisia (31.9%), and Oman (24.9%). Levant countries showed moderate fractions: Palestine (18.2%), Lebanon (15.4%), Syria (15.5%), and Jordan (13.7%). Gulf countries exhibited minimal PAFs: Bahrain (0.25%), Kuwait (0.44%), and Qatar (1.76%). Narrow confidence intervals for Egypt, Morocco, and Lebanon (± 0.5 -1.5 percentage points) indicated stable estimates, while broader intervals for Yemen (± 6.0 percentage points) and Algeria (± 5.8 percentage points) reflected temporal volatility.

-----Insert Figure 8 here -----

Population attributable fraction decomposition revealed pathway-specific temporal dynamics (Figure 9A). Egypt maintained stable combined PAF throughout (47.1% in 2010 $\rightarrow$ 46.5% in 2023), with environmental PAF constituting 96.2% of the total (environmental: 45.3-45.8%, occupational: 2.1-3.4%). Morocco exhibited gradual PAF decline (41.1% $\rightarrow$ 37.8%) driven by occupational pathway reduction (5.4% $\rightarrow$ 4.1%). Tunisia demonstrated pronounced volatility (PAF range: 28.2-33.8%) with a 2012 spike to 33.8% environmental PAF. Yemen showed dramatic temporal patterns: PAF escalated from 36.3% (2010) to 50.9% peak (2013), declined sharply to 33.8% (2017), then resurged to 48.9% (2023). Cross-sectional analysis revealed modest positive correlation between environmental and occupational PAF (Figure 9B; Spearman $\rho = 0.47$, $p < 0.001$).

-----Insert Figure 9 here -----

PD burden demonstrated an apparent inverse association with pesticide application intensity across all 18 MENA countries (Figure 10; Spearman $\rho = -0.33$, $p = 0.18$), though sensitivity analysis excluding Gulf countries with capital-intensive agriculture revealed this relationship was not statistically robust ($\rho = -0.13$, $p = 0.73$; Supplementary Figure 5). Morocco achieved the highest PD burden rate (31.5 DALYs per 100,000) at moderate intensity (1.82 kg/ha), followed by Tunisia (21.4 per 100,000 at 1.08 kg/ha) and Egypt (20.0 per 100,000 at 3.86 kg/ha), while Kuwait (0.11 per 100,000 at 175.4 kg/ha), Bahrain (0.08 per 100,000 at 7.89 kg/ha), and Qatar (0.26 per 100,000 at 68.4 kg/ha) demonstrated minimal PD burden despite 22-1,750 fold higher intensities. The regression slope of -2.1 DALYs per 100,000 per $\log_{10}(\text{kg/ha})$ indicated that each 10-fold intensity increase corresponded to a 2.1 DALYs per 100,000 decrease in PD burden, though the wide confidence interval and non-significant p-value reflected high between-country variance.

-----Insert Figure 10 here -----

At the MENA aggregate level, pesticide exposure accounted for 54,979 attributable PD DALYs annually (95% CI: 49,390-60,568; PAF 28.9%) out of total PD burden of 190,368 DALYs/year (Figure 11). The MENA per-capita attributable rate (13.7 DALYs per 100,000) was substantially lower than the global rate (35.3 per 100,000; 95% CI: 33.9-36.7), with global PAF reaching 42.4% (2,686,385 attributable DALYs annually out of 6,364,907 total DALYs).

-----Insert Figure 11 here -----

The relationship between total PD burden from all causes and pesticide-attributable PD burden revealed substantial cross-country variation in population attributable fractions (Figure 12), with Egypt, Yemen, and Morocco demonstrating the highest PD attributable fractions (46.9%, 45.6%, and 39.1% respectively), while Gulf countries exhibited minimal attributable fractions (<2%), reflecting low baseline PD burden and negligible exposure prevalence.

-----Insert Figure 12 here -----

Life-Course Distribution and Age Standardization

The life-course distribution of pesticide-attributable neurological burden revealed a bimodal pattern (Figure 13). ID dominated burden during the first five decades: the 0-4 year age group carried the highest absolute burden (mean 73,978 DALYs/year; 95% CI: 70,736-77,220), representing 100% of pesticide-attributable burden in this age group. ID remained the exclusive contributor through age 15-19 (49,683 DALYs/year), with PD contributing <0.01% before age 20. PD reached parity with ID at ages 70-74 (52.4% PD vs 47.6% ID) and became dominant in the 75+ group (72.3% PD vs 27.7% ID), where absolute PD burden reached 16,918 DALYs/year (95% CI: 15,218-18,619).

-----Insert Figure 13 here -----

Age-specific DALY rates showed broadly stable ID rates across the lifespan (range: 119-153 per 100,000), while PD rates rose steeply with age from near zero below age 45 to 329 per 100,000 in the 75+ group. The cumulative life-course perspective illustrated compounding ID burden: by age 75+, cumulative ID burden reached 531,277 DALYs versus cumulative PD burden of 37,052 DALYs. Three age groups bore disproportionate burden relative to population size: ages 60-64 (burden/population ratio 1.13), 65-69 (ratio 1.44), 70-74 (ratio 1.92), and 75+ (ratio 3.23). Statistical comparisons of disease-specific burden rates across MENA subregions are provided in Table 3.

Table 3. Subregional and Disease-Specific Burden Stratification with Statistical Comparisons, 2010-2023

Subregion	PD_Rate_CI	ID_Rate_CI	Total_Rate_CI	ID_PD_Ratio_Formatted	p_value_formatted
Other	5.8 (5.3-6.3)	107.2 (99-115.4)	113 (104.3-121.6)	18.5:1	<0.001
North Africa	18.4 (17.2-19.7)	137.3 (130.3-144.3)	155.7 (149.5-161.9)	7.4:1	<0.01
Levant	6.9 (6.7-7.2)	123.5 (119.5-127.5)	130.4 (126.5-134.4)	17.9:1	<0.001
Gulf	6.9 (6.7-7)	117.9 (111.4-124.3)	124.7 (118.3-131.2)	17.2:1	<0.001

Age standardization had markedly different effects on PD and ID burden estimates (Figure 14). For PD, ASR/crude ratios exceeded 1.0 in 13 of 18 countries, indicating that crude rates systematically underestimate burden in populations younger than the WHO World Standard Population. Among countries with representative age structures, ratios ranged from 1.10 in Egypt to 2.37 in Palestine. Crude PD rates exceeded age-standardized rates in Morocco (ratio 0.67), Tunisia (0.63), and Algeria (0.89). For ID, ASR/crude ratios clustered tightly around 1.0 across nearly all countries (interquartile range 0.97-1.03), with exceptions in Sudan (1.21) and Iraq (1.35).

-----Insert Figure 14 here -----

Palestine carried the highest mean age-standardized burden (235.7 per 100,000; 95% CI: 226.4-245.0), followed by Yemen (232.6; 211.4-253.8) and Egypt (200.4; 191.1-209.6), all substantially exceeding the global reference rate of 161.2 per 100,000 (Figure 15A). ID contributed 84-96% of age-standardized totals across the top nine countries. Subregional analysis revealed distinct patterns (Figure 15B): the Levant demonstrated widest dispersion, North Africa showed compact distribution near global reference, the Gulf exhibited lowest mean burden, and Other MENA displayed extreme bimodal distribution driven by Yemen's high burden and Iraq's censored estimates.

-----Insert Figure 15 here -----

Temporal Dynamics

The MENA region's aggregate pesticide-attributable neurological burden increased 27.5% from 474,328 DALYs (2010) to 604,845 DALYs (2023), with a peak of 595,008 DALYs in 2022 (Figure 16A). Children and adolescents under 20 years contributed approximately 45% of total MENA DALYs in 2010, declining modestly as regional birth rates stabilized. The 75+ age group burden nearly doubled from 16,072 DALYs (2010) to 30,899 DALYs (2023).

Age-specific burden patterns across countries revealed marked heterogeneity (Figure 16B). Yemen carried the highest mean total burden across age groups (rates exceeding 260 per 100,000 in 0-4, 5-9, and 10-14 year bands, reaching 440 per 100,000 at 75+). Palestine ranked second with elevated rates across nearly all age groups (196-256 per 100,000 for ages 0-74, rising to 349 per 100,000 at 75+). Egypt and Morocco exhibited strong positive age gradients, with Morocco peaking at 775 per 100,000 at 75+. Gulf states occupied the lowest burden range, with Qatar's rates ranging 45-91 per 100,000 across all age groups.

-----Insert Figure 16 here -----

Temporal trend analysis revealed divergent trajectories across subregions (Figure 17). In the Gulf, ID burden declined 22% from 114.7 per 100,000 (2010) to 89.6 per 100,000 (2023), while PD remained stable. The Levant maintained elevated ID burden throughout, declining from 162.4 per 100,000 (2010) to 134.2 per 100,000 (2023). North Africa demonstrated variable trajectory, with ID burden rising from 118.9 per 100,000 (2010) to a 2012 peak of 143.7 per 100,000, then declining to 115.5 per 100,000 (2023). Individual country trajectories showed distinct patterns: Palestine maintained the highest burden at every time point (260.2 per 100,000 in 2010, declining to 205.9 in 2023), while Syria exhibited U-shaped trajectory with a 2018 trough.

-----Insert Figure 17 here -----

Model Validation and Internal Consistency Checks

Correlation analysis across 252 country-year observations was conducted to assess the internal consistency of the burden estimation model. These analyses test whether the model's mathematical structure produces self-consistent results over time and across countries, rather than representing independent empirical discoveries. Spearman rank correlation analysis revealed coherent internal structure among exposure and burden metrics (Supplementary Figure 2). Agricultural employment and rural population were strongly associated ($\rho = 0.754$, $p < 0.001$), while pesticide intensity showed inverse correlations with both ($\rho = -0.577$ and -0.684 respectively, $p < 0.001$), reflecting the decoupling of chemical intensity from labor intensity in mechanized agricultural systems. As expected given that neurodevelopmental burden constitutes 90% of total DALYs, total burden and neurodevelopmental burden were nearly perfectly correlated ($\rho = 0.986$, $p < 0.001$).

Temporal consistency checks using lagged exposure-response models were performed to assess whether the model produces stable burden estimates across different temporal assumptions. Lagged exposure-response analysis using 3-year lags demonstrated significant positive within-

country temporal correlations in four countries—Oman ($\rho = 0.773$, $p = 0.005$), Lebanon ($\rho = 0.670$, $p = 0.024$), Egypt ($\rho = 0.636$, $p = 0.035$), and Qatar ($\rho = 0.609$, $p = 0.047$)—indicating that years with elevated pesticide intensity were followed by increased burden three years later (Supplementary Figure 3). Lag sensitivity analysis across 0-7 year lags showed that ID associations peaked at lag 0 ($R^2 = 0.202$) and declined monotonically with increasing lag, while PD associations remained stable across all lags ($R^2 = 0.260$ - 0.271), confirming that the inverse intensity-PD relationship is a persistent structural feature rather than temporally specific (Supplementary Figure 4).

Uncertainty Quantification

Sensitivity analysis revealed that base case estimates were robust in central trajectory but subject to substantial absolute uncertainty (Figure 18). The uncertainty ratio (upper bound/lower bound) ranged from 3.09 (2023) to 3.40 (2015), consistently exceeding the 2.0 high-sensitivity threshold (Table 4). The ratio declined gradually over time, indicating modest narrowing of proportional uncertainty.

-----Insert Figure 18 here -----

Table 4. Annual uncertainty decomposition by parameter (2010-2023)

Year	Base_Case_DALYs	Beta_Percent	Exp_Percent	RR_Percent	Uncertainty_Ratio
2010	474328	-69	3.2	0.4	3.24
2011	544354	-69.6	3.2	0.4	3.31
2012	561252	-69.4	3.2	0.4	3.29
2013	578511	-69.4	3.1	0.4	3.29
2014	590544	-69.7	3.2	0.4	3.32
2015	576581	-70.5	3.3	0.4	3.4
2016	549662	-68.6	3.5	0.4	3.2
2017	546614	-69.4	3.8	0.4	3.27
2018	581776	-69.1	3.8	0.4	3.24
2019	583179	-68.7	4	0.4	3.21
2020	587024	-68.7	4.2	0.4	3.21
2021	582925	-68.5	4.4	0.4	3.17
2022	595008	-67.9	4.7	0.5	3.12
2023	604845	-67.6	4.8	0.5	3.09

Notes: Base case represents MENA aggregate burden using central parameter values. Beta $\pm\%$ indicates the percentage change in total burden when IQ shift coefficient varied from lower to upper 95% confidence interval (-0.96 to -3.91 IQ points per ln unit). Exposure $\pm\%$ represents combined contribution of occupational (60-90%) and environmental (20-45%) exposure prevalence variation. RR $\pm\%$ indicates contribution of PD RR uncertainty (occupational: 1.3-1.7). Uncertainty ratio calculated as upper bound divided by lower bound; values >2.0 indicate high parameter sensitivity.

Parameter decomposition across top burden countries demonstrated the complexity of uncertainty attribution (Figure 19). The negative beta contributions observed across all three countries (-99.2% in Egypt, -64.4% in Morocco, -79.4% in Yemen) arose from the inverse mathematical relationship between the IQ shift coefficient and total burden under capped conditions: when IQ shifts are capped at 9.0 points, lowering the beta coefficient paradoxically increases estimated burden by reducing the number of years requiring capping, thereby increasing effective exposure-response sensitivity. This counterintuitive relationship reflects the methodological constraint imposed by the biological plausibility cap rather than traditional parameter sensitivity. In practical terms, beta coefficient uncertainty remains the dominant source of total uncertainty range (absolute contributions: 133,071 DALYs in Egypt, 38,127 DALYs in Morocco, 61,619 DALYs in Yemen), though the direction of effect reverses under capping. Exposure prevalence assumptions contributed positively in all countries (6.0% in Egypt, 29.0% in Morocco, 43.7% in Yemen), with Yemen showing highest sensitivity due to its large rural population and balanced contribution from both pathways. Relative risk for PD contributed 4.1% in Egypt, rising to 43.0% in Yemen despite PD constituting a smaller fraction of total burden (4.0% vs 10.2% in Egypt), reflecting Yemen's higher absolute PD uncertainty in the context of smaller total burden.

-----Insert Figure 19 here -----

Discussion

This study provides the first comprehensive quantification of pesticide-attributable neurological burden across the MENA region, revealing that an estimated 568,329 DALYs occur annually from combined neurodevelopmental and neurodegenerative impacts. Our findings demonstrate that pesticide exposure constitutes a substantial but previously unquantified public health burden in MENA agricultural communities, with three countries—Egypt, Yemen, and Algeria—accounting for 61% of the regional total despite representing only 32% of the population (Table 1). The dominance of neurodevelopmental burden (90% of total DALYs) challenges conventional occupational health paradigms that prioritize adult worker protection, instead highlighting prenatal and early-life exposure as the critical intervention window.

-----Insert Table 1 here -----

To contextualize these findings, we compared pesticide-attributable burden to other environmental risks quantified in GBD estimates for the MENA region. In 2021, ambient particulate matter pollution accounted for 2,399 age-standardized DALYs per 100,000 population in MENA [62], while lead exposure contributed 489 age-standardized DALYs per 100,000 in 2019 [63]. Our estimated age-standardized pesticide burden of 143 DALYs per 100,000 represents approximately 29% of lead exposure burden, positioning pesticides as a substantial but previously unquantified environmental health determinant. However, unlike air pollution and lead—which have received substantial policy attention and regulatory investment—pesticide neurotoxicity remains largely unaddressed in regional health agendas [64].

Globally, our findings align with emerging evidence that environmental chemical exposures contribute substantially to neurodevelopmental disorders. Grandjean and Landrigan (2014) have argued that exposures to industrial chemicals contribute to a pandemic of developmental neurotoxicity, with organophosphate pesticides identified as priority contributors [65]. Economic analyses quantify the magnitude of this burden: Attina et al. (2016) estimated that disease costs attributable to endocrine-disrupting chemicals in the United States totaled approximately 340 billion (2010US), with organophosphate pesticides alone accounting for \$42 billion—comparable to the estimated costs of childhood lead exposure in the same period [66]. Our MENA estimates extend this evidence base to low- and middle-income agricultural regions where pesticide use intensity and the burden of acute poisoning often exceed high-income countries while regulatory safeguards remain weaker [64]. The magnitude of per-capita burden we observe in Palestine (229 DALYs per 100,000) and Yemen (235 DALYs per 100,000) approaches that documented for lead exposure in highly contaminated populations (489 DALYs per 100,000 MENA aggregate; [63]), yet pesticide-attributable burden receives a fraction of the policy attention and intervention investment directed toward lead remediation, underscoring the urgency of pesticide policy reform.

Biological Mechanisms and Consistency with Experimental Evidence

The neurodevelopmental impacts we quantified align with extensive experimental evidence demonstrating organophosphate neurotoxicity through multiple mechanisms beyond acetylcholinesterase inhibition. Prenatal and early postnatal organophosphate exposure disrupts the immune system [3], gene expression and epigenetics [67] and neurodevelopmental processes including neurogenesis, cell differentiation, synaptogenesis, and neurotransmitter system maturation [68]. Critical windows of vulnerability occur during rapid brain development when even low-level exposures can produce permanent architectural changes to neural circuitry [69]. The logarithmic dose-response relationship we observed is consistent with receptor-mediated toxicity operating across concentration ranges typical of agricultural exposure [70].

For Parkinson's disease (PD), the biological plausibility of pesticide causation is supported by convergent evidence from animal models, in vitro studies, and human autopsy material. Organophosphates and other pesticides induce mitochondrial dysfunction, oxidative stress, protein aggregation, and dopaminergic neurodegeneration in experimental systems [71]. Paraquat—widely used in MENA agriculture—structurally resembles MPTP, a known PD-inducing toxin, and produces selective dopaminergic neurotoxicity in rodent models [53]. The 10-30 year lag between cumulative exposure and clinical manifestation we assumed is consistent with the progressive neurodegenerative pathology characteristic of PD [11].

The Mechanization Paradox and Agricultural Structure

The apparent inverse relationship between pesticide application intensity and PD burden observed across all 18 MENA countries ($\rho = -0.33$, $p = 0.18$)—whereby Kuwait (175 kg/ha) exhibits 313-fold lower per-capita PD burden than Morocco (1.8 kg/ha)—reflects structural differences in agricultural labor organization rather than biological dose-response. Sensitivity analysis excluding Gulf countries with capital-intensive greenhouse agriculture reversed the correlation direction ($\rho = +0.28$, $p = 0.36$), while analysis restricted to 9 traditional agricultural

economies (North Africa and Levant, excluding conflict-affected countries) showed no significant intensity-burden relationship ($\rho = -0.13$, $p = 0.73$; Supplementary Figure 5). This demonstrates that the observed inverse pattern is an ecological confounding artifact driven by Gulf mechanization rather than a generalizable epidemiological phenomenon.

Gulf countries employ capital-intensive greenhouse agriculture with minimal permanent workforces (predominantly temporary migrant laborers with short tenure), while North African countries maintain labor-intensive field agriculture with multigenerational farmworker populations experiencing decades of cumulative exposure [72]. This pattern has critical policy implications: national burden estimates may mask extreme individual-level risks in small but highly exposed subpopulations, particularly migrant agricultural workers who are often excluded from occupational health surveillance and protections [73].

Sensitivity analysis revealed that this inverse PD-intensity relationship was driven primarily by inclusion of Gulf countries with capital-intensive agricultural systems (Supplementary Figure 5). When Gulf countries were excluded from analysis, the relationship direction reversed ($\rho = +0.28$, $p = 0.36$), though remained non-significant. Among 9 'core MENA' countries with traditional labor-intensive agriculture (North Africa and Levant, excluding conflict-affected Iraq, Yemen, and Sudan), pesticide intensity showed no association with PD burden ($\rho = -0.13$, $p = 0.73$). For example, Morocco (1.8 kg/ha) exhibited 5.4-fold higher PD burden (31.5 per 100,000) than Palestine (27.2 kg/ha, 15-fold higher intensity; 5.8 per 100,000), reflecting differences in workforce age structure and exposure duration rather than intensity per se. This pattern indicates that national PD burden is determined primarily by the proportion of population engaged in agriculture and cumulative exposure duration, rather than per-hectare application rates.

The environmental exposure pathway contributed most substantially in two countries—Egypt (37% of combined PAF) and Yemen (44%)—reflecting dispersed smallholder agricultural systems where pesticide storage, mixing, and application occur in close proximity to residences. Biomonitoring studies in similar agricultural contexts document household contamination in 73–89% of farmworker residences through take-home pathways, peridomestic use, and drift [74]. This finding supports differentiated intervention strategies: household-level measures (improved storage, residential setbacks, educational programs) in dispersed agriculture regions versus farm-level engineering controls and personal protective equipment in consolidated operations [75].

Temporal Patterns and Policy Context

The 27.5% increase in regional burden from 2010 to 2023 occurred despite declining agricultural employment (7.0% to 4.9% of workforce) and rural population (43.5% to 40.2%), indicating that pesticide intensity increases may have outpaced labor mechanization in driving population health impacts or introduction of more neurotoxic pesticides. Individual country temporal patterns provide instructive case studies in agricultural transition dynamics. Algeria's 219% burden increase coincided with documented agricultural modernization initiatives that increased mechanized pesticide application without commensurate worker protection improvements [76]. Yemen's burden escalated 132% during civil conflict (2010–2023), potentially reflecting disruption of agricultural extension services, collapse of pesticide regulation enforcement, and population displacement to subsistence farming [77].

In contrast, Qatar achieved 75% reduction in pesticide application intensity (208 to 52 kg/ha) through adoption of integrated pest management in greenhouse operations, demonstrating feasibility of intensive production with reduced chemical reliance [78]. However, this intensity reduction produced minimal population health benefit given Qatar's negligible agricultural employment, highlighting that intensity reduction alone is insufficient without addressing exposure pathway prevalence.

Regulatory Landscape and Policy Implications

Developing countries including MENA region operate diverse pesticide regulatory frameworks ranging from comprehensive to minimal oversight, with enforcement capacity often constrained by resource limitations and institutional fragmentation [79]. Most countries lack pesticide residue monitoring programs, occupational exposure surveillance, or pesticide poisoning registries, creating data gaps that impede evidence-based policymaking [80]. Most MENA developing countries permitting use of compounds prohibited in European Union and North American markets [79].

Evidence-based policy priorities emerging from our findings include: (1) Phased prohibition of WHO Class I pesticides, following precedent from European Union Regulation (EC) No 1107/2009 which demonstrated feasibility of hazard-based restrictions without compromising agricultural productivity [81]. Cost-benefit analyses in high-income settings show that organophosphate restrictions generate substantial health co-benefits exceeding agricultural adaptation costs [66]. (2) Mandatory buffer zones between agricultural applications and residences, schools, and water sources. California's 2017 regulations requiring quarter-mile buffers for chlorpyrifos [82], and 0.4 km of schools and childcare [83] facilities reduced ambient exposure significantly in nearby residences without affecting crop yields. (3) Occupational health programs targeting pesticide applicators, including medical surveillance, biomonitoring, and protective equipment provision. Occupational health impacts for pesticide applicators have improved significantly following the adoption of Bt cotton in India. Research shows that the technology reduced pesticide applications by 50%, with a 70% reduction in the use of the most toxic chemicals, leading to a notable decline in acute poisoning incidence [84].

Study Strengths and Limitations

This study has several methodological strengths. First, we employed a comprehensive lifespan approach integrating both neurodevelopmental and neurodegenerative outcomes within a unified burden estimation framework, capturing the full temporal spectrum of pesticide neurotoxicity from prenatal exposure through elderly populations. Second, our use of country-specific exposure prevalence estimates derived from agricultural employment and rural population distributions, rather than uniform regional assumptions, enabled heterogeneity in burden patterns to emerge and identified high-risk populations that would be masked by aggregate analyses. Third, we applied exposure-response coefficients and relative risk estimates from prospective epidemiological studies [6] and meta-analyses rather than relying on cross-sectional associations, strengthening causal inference despite the ecological nature of our exposure metrics. Fourth, comprehensive sensitivity analyses demonstrated that findings were robust to parameter uncertainty despite 3-fold uncertainty ranges, with core conclusions remaining valid across

plausible epidemiological scenarios. Finally, our 14-year temporal analysis (2010-2023) captured both baseline burden patterns and emerging trends, revealing Algeria's 219% increase and Qatar's 75% pesticide intensity reduction, demonstrating the feasibility of burden reduction through policy intervention.

Despite those strengths, we do have some limitations. Our neurodevelopmental burden estimates rely on ecological pesticide application intensity as a proxy for individual prenatal exposure, an assumption that introduces substantial uncertainty. The quantitative relationship between regional kilograms per hectare and maternal urinary organophosphate metabolite concentrations remains empirically unestablished. Individual exposure depends on residential proximity, household pesticide use, occupational pathways, dietary consumption patterns, and temporal variability—factors not captured in aggregate agricultural statistics [5]. We applied organophosphate-specific intelligence quotient (IQ) coefficients to total pesticide use data that include herbicides, fungicides, and other chemical classes with potentially different neurodevelopmental toxicity profiles. To the extent non-organophosphate compounds dominate national pesticide mixes, our estimates may overstate neurodevelopmental burden [85]. Conversely, if neurotoxic compounds beyond organophosphates (e.g., neonicotinoids, pyrethroids) contribute substantially to MENA pesticide use, our estimates may be conservative. Without pesticide class composition data for the study period, the direction and magnitude of this bias remain uncertain.

The biological plausibility cap at 9.0 IQ points—corresponding to the Bouchard et al. (2011) upper confidence interval—applied to 15 countries across 63 country-years, affecting 24% of observations [6]. This methodological constraint, while necessary to avoid implausible extrapolation beyond observed exposure ranges, introduces nonlinearity in dose-response relationships at extreme intensities. Countries exceeding the cap (Kuwait: 1,754-fold above reference) may experience actual neurodevelopmental impacts beyond what our conservative estimates reflect, particularly if individual exposures in highly exposed subgroups exceed population averages.

For PD, we assumed relative risks derived from predominantly Western cohorts ($RR=1.5$ occupational, 1.25 environmental) apply uniformly across MENA populations despite potential genetic, dietary, comorbidity, and co-exposure differences that may modify susceptibility. MENA-specific epidemiological research on pesticide-PD associations is notably absent, limiting ability to validate or calibrate model parameters. The 10-30 year cumulative exposure duration we assumed for PD manifestation may not adequately capture risk in populations with early-life agricultural employment onset typical of family farming systems.

Iraq's censored burden estimates (attributable DALYs set to zero during 8 years when pesticide intensity fell below 0.1 kg/ha) reflect data quality issues during conflict rather than true absence of neurodevelopmental risk. Conflict-affected populations may experience elevated pesticide exposure through disrupted regulation, use of prohibited compounds, and deterioration of application safety practices.

We calculated combined occupational and environmental population attributable fractions using multiplicative formulas, which assume independent exposures. However, in agricultural

populations where farmworkers reside in rural areas near application sites, exposure pathways may overlap. Sensitivity analysis comparing multiplicative, additive, and overlap-corrected PAF formulations revealed minimal impact on burden estimates (regional difference <0.5%; Table 5), indicating that the independence assumption does not materially affect our findings.

Table 5. Sensitivity Analysis of Population Attributable Fraction Calculation Methods for Parkinson's Disease

Country	Multiplicative PAF (%) ^a	Overlap-Corrected PAF (%) ^b	Difference (%)	Current Burden (DALYs)	Burden Impact (DALYs) ^c
Egypt	46.9	47.5	-0.5	20,687	-241
Yemen	45.6	46.0	-0.4	3,121	-27
Morocco	39.1	39.6	-0.5	11,156	-137
Tunisia	31.9	32.0	-0.1	2,484	-8
Algeria	25.4	25.4	0.0	6,951	3
Sudan	17.4	16.9	0.5	2,692	80
Lebanon	15.4	15.1	0.2	554	8
Libya	14.6	14.3	0.3	523	11
Regional Mean	23.5	23.5	<0.1	54,979	-82

Notes:

^a *Multiplicative formula: $PAF_{combined} = 1 - (1 - PAF_{occup})(1 - PAF_{environ})$, assumes independent exposures*

^b *Overlap-corrected: $PAF_{combined} = PAF_{occup} + PAF_{environ} - PAF_{overlap}$, where $overlap = \min(P_{occup}, P_{environ})$*

^c *Negative values indicate multiplicative formula slightly underestimates burden; positive values indicate slight overestimation*

Future Research Directions

Advancing burden estimation methodology requires region-specific prospective birth cohort studies with biomarker-based prenatal exposure assessment and standardized neurodevelopmental testing at multiple ages, similar to cohorts conducted in US, Mexico, and Ecuador [86]. Such studies should include comprehensive pesticide class characterization beyond organophosphates to quantify contributions of pyrethroids, neonicotinoids, and other compounds. Economic valuation studies quantifying productivity losses from IQ decrements would strengthen policy case for prevention investments. For PD, MENA-specific case-control studies with retrospective occupational exposure assessment and genetic susceptibility profiling would refine relative risk estimates and identify high-risk subpopulations.

Improved exposure assessment infrastructure is essential. Remote sensing technologies and geographic information systems can map pesticide application zones relative to residential areas, schools, and water sources to characterize population-level exposure gradients [83]. Sentinel site biomonitoring programs in high-burden countries could establish relationships between ecological intensity metrics and individual biomarker concentrations, enabling calibration of burden models. National pesticide poisoning surveillance systems should be integrated with occupational health and healthcare systems to enable real-time risk assessment.

Intervention research should evaluate feasibility, acceptability, and effectiveness of alternative pest management strategies adapted to MENA agricultural contexts. Farmer field school programs promoting integrated pest management have demonstrated a mean pesticide reduction to 30.7% of baseline with a 40.9% yield increase in Asian and African settings [87]. Community-based participatory research approaches engaging farmworker communities, agricultural extension agents, and health providers could identify culturally appropriate and economically viable risk reduction strategies. Economic incentives for adopting low-toxicity alternatives—similar to EU organic agriculture subsidies—merit pilot testing and rigorous evaluation.

Conclusions

This analysis establishes pesticide exposure as a substantial contributor to neurological disease burden in MENA agricultural populations, generating an estimated 568,329 DALYs annually with impacts concentrated in countries combining intensive pesticide use with large agricultural workforces or dispersed rural populations. The predominance of neurodevelopmental burden (90% of total DALYs) identifies prenatal and early-life periods as critical intervention windows, requiring policy approaches that transcend conventional occupational health frameworks focused on adult worker protection. The mechanization paradox—whereby high-intensity Gulf systems generate low population burden but potentially extreme individual risks in migrant worker populations—demands policy addressing both population-average exposures and within-country inequalities. Reducing burden requires coordinated action across hazard-based restrictions on highly hazardous pesticides (WHO Class Ia/Ib, including organophosphates such as parathion and methamidophos, and carbamates such as carbofuran and aldicarb), spatial planning interventions including buffer zones, occupational health programs providing medical surveillance and protective equipment, agricultural extension programs supporting integrated pest management adoption, and strengthened surveillance systems enabling data-driven risk assessment. The gap between MENA pesticide burden (143 DALYs per 100,000 age-standardized) and high-income regions with stricter regulations suggests substantial burden reduction is achievable through policy harmonization and enforcement strengthening, though intervention success depends critically on addressing root determinants including farmworker poverty, power asymmetries between employers and workers, weak governance in pesticide

Declarations

Ethics Approval and Consent to Participate

Human Ethics and Consent to Participate declarations: not applicable.

This study used publicly available aggregate-level data and did not involve human participants, human tissue, or animals. No ethical approval was required as the research did not involve direct interaction with human subjects, and no informed consent was necessary.

Consent for Publication

Not applicable.

Author Contributions

AD and AS: Conceptualization, Methodology, Investigation, Writing—Original Draft, Writing—Review & Editing, Validation. JA: Investigation, Resources, Writing—Review & Editing,

Validation. AA: Investigation, Resources, Writing—Review & Editing, Validation. SS: Investigation, Resources, Writing—Review & Editing, Validation. BÅ: Data Curation, Formal Analysis, Writing—Review & Editing. MS: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing—Original Draft, Writing—Review & Editing, Visualization, Project Administration, Funding Acquisition, Supervision. All authors (Aya Darwish, Aya Samy, Ahmed Amin, Jana Al-Nady, Shima Sami, Balázs Ádám, Moustafa Sherif) have read and approved the final manuscript.

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Data Availability Statement

All data used in this study are publicly available from the following sources: pesticide use data from the Food and Agriculture Organization Corporate Statistical Database (FAOSTAT; <https://www.fao.org/faostat/>), population data from the United Nations World Population Prospects 2024 revision (<https://population.un.org/>), agricultural employment data from Our World in Data (<https://ourworldindata.org/>), and baseline disease burden data from the Global Burden of Disease Study 2023 (<https://vizhub.healthdata.org/gbd-results/>). Country-specific calculated burden estimates and analysis code are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at [xx]

Supplementary Figure S1. Literature validation of pesticide exposure prevalence assumptions using biomonitoring studies.

Supplementary Figure S2. Spearman rank correlations among independent pesticide exposure and burden metrics across MENA countries, 2010–2023.

Supplementary Figure S3. Temporal exposure-response relationships between 3-year lagged pesticide intensity and neurological burden across MENA countries, 2010–2023.

Supplementary Figure S4. Lag sensitivity analysis showing model fit (R^2) by exposure lag period (0–7 years) for three neurological burden outcomes.

Supplementary Figure S5. Sensitivity analysis of Parkinson's disease-pesticide intensity relationship across MENA countries under four analysis scenarios.

Competing Interests

The authors declare that they have no competing interests.

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Table 1. Country-Specific Pesticide-Attributable Neurological Burden with Temporal Trends and Age Standardization, 2010-2023

Subregion	Country	Mean Total DAL Ys	95% CI	Mean Crude Rate	SD Crude Rate	Mean ASR	ASR/Crude Ratio	Mean PD DAL Ys	PD %	Mean Neuro dev YLDs	Neuro dev %	Temporal Change
Gulf	Bahrain†	1,421	(1,390 – 1,453)	102.4	8.5	101.6	0.99	1	0.1 %	1,420	99.9%	+4.1%
Gulf	Kuwait†	3,946	(3,757 – 4,136)	102.4	22.0	103.2	1.01	4	0.1 %	3,942	99.9%	-11.1%
Gulf	Oman	6,222	(5,888 – 6,557)	151.1	13.6	158.3	1.05	373	6.0 %	5,849	94.0%	+33.9 %
Gulf	Qatar†	1,832	(1,710 – 1,954)	75.2	4.8	77.9	1.04	6	0.3 %	1,826	99.7%	+53.7 %
Gulf	Saudi Arabia	42,149	(40,679 – 43,619)	142.8	13.6	151.6	1.06	2,868	6.8 %	39,281	93.2%	+4.1%

Subregion	Country	Mean Total DAL Ys	95% CI	Mean Crude Rate	SD Crude Rate	Mean ASR	ASR/Crude Ratio	Mean PD DAL Ys	PD %	Mean Neuro dev YLDs	Neuro dev %	Temporal Change
Gulf	United Arab Emirates	6,880	(6,595 – 7,165)	78.6	5.5	73.4	0.93	208	3.0 %	6,671	97.0%	+36.9 %
Gulf	Gulf Subtotal	62,451	(60,450 – 64,452)	124.7	12.3	129.9	1.04	3,462	5.5 %	58,989	94.5%	+10.2 %
Levant	Jordan	16,599	(16,004 – 17,193)	175.0	17.8	171.0	0.98	518	3.1 %	16,081	96.9%	+15.5 %
Levant	Lebanon	8,041	(7,610 – 8,473)	138.7	7.3	137.3	0.99	554	6.9 %	7,487	93.1%	+2.2%
Levant	Palestine	10,675	(10,534 – 10,817)	228.9	17.8	235.7	1.03	275	2.6 %	10,401	97.4%	+6.3%
Levant	Syria	18,434	(16,659 – 20,209)	86.5	10.7	87.9	1.02	1,513	8.2 %	16,922	91.8%	+3.2%
Levant	Levant Subtotal	53,749	(52,714 – 54,785)	130.4	7.5	130.8	1.00	2,859	5.3 %	50,890	94.7%	+7.2%
North Africa	Algeria	65,223	(57,474 – 72,973)	158.5	38.6	158.2	1.00	6,951	10.7 %	58,273	89.3%	+219.4 %
North Africa	Egypt	203,275	(198,172 – 208,379)	200.1	19.7	200.4	1.00	20,687	10.2 %	182,588	89.8%	+5.7%
North Africa	Libya	9,062	(8,078 – 10,045)	135.3	30.4	134.2	0.99	523	5.8 %	8,539	94.2%	-15.8%

Subregion	Country	Mean Total DAL Ys	95% CI	Mean Crude Rate	SD Crude Rate	Mean ASR	ASR/Crude Ratio	Mean PD DAL Ys	PD %	Mean Neuro dev YLDs	Neuro dev %	Temporal Change
North Africa	Morocco	59,163	(58,815–59,512)	168.5	6.9	168.5	1.00	11,156	18.9%	48,007	81.1%	+2.5%
North Africa	Sudan	18,003	(13,075–22,931)	41.2	18.4	48.9	1.19	2,692	15.0%	15,311	85.0%	+138.0%
North Africa	Tunisia	16,374	(15,496–17,251)	142.0	15.3	139.0	0.98	2,484	15.2%	13,889	84.8%	+14.3%
North Africa	North Africa Subtotal	371,100	(360,436–381,764)	155.7	11.8	157.0	1.01	44,493	12.0%	326,607	88.0%	+23.6%
Other MENA	Iraq†‡	3,413	(1,200–5,626)	9.7	13.6	12.4	1.27	1,044	30.6%	2,369	69.4%	-68.1%
Other MENA	Yemen	77,615	(67,372–87,859)	234.6	40.4	232.6	0.99	3,121	4.0%	74,495	96.0%	+132.2%
Other MENA	Other MENA Subtotal	81,028	(71,590–90,467)	113.0	16.5	113.5	1.00	4,165	5.1%	76,863	94.9%	+82.4%
MENA Total	MENA Total	568,329	(551,166–585,492)	141.7	8.9	143.3	1.01	54,979	9.7%	513,349	90.3%	+27.5%

Notes: Mean of 14 annual estimates (2010-2023). † Near-absent agricultural workforce. ‡ Iraq: Intellectual disability burden censored to zero during 2013-2020 (8 of 14 years) when pesticide application intensity fell below 0.1 kg/ha reference threshold. Mean values represent averages across all 14 years, including both censored (PD-only) and uncensored years. Iraq included in 18-country regional total.

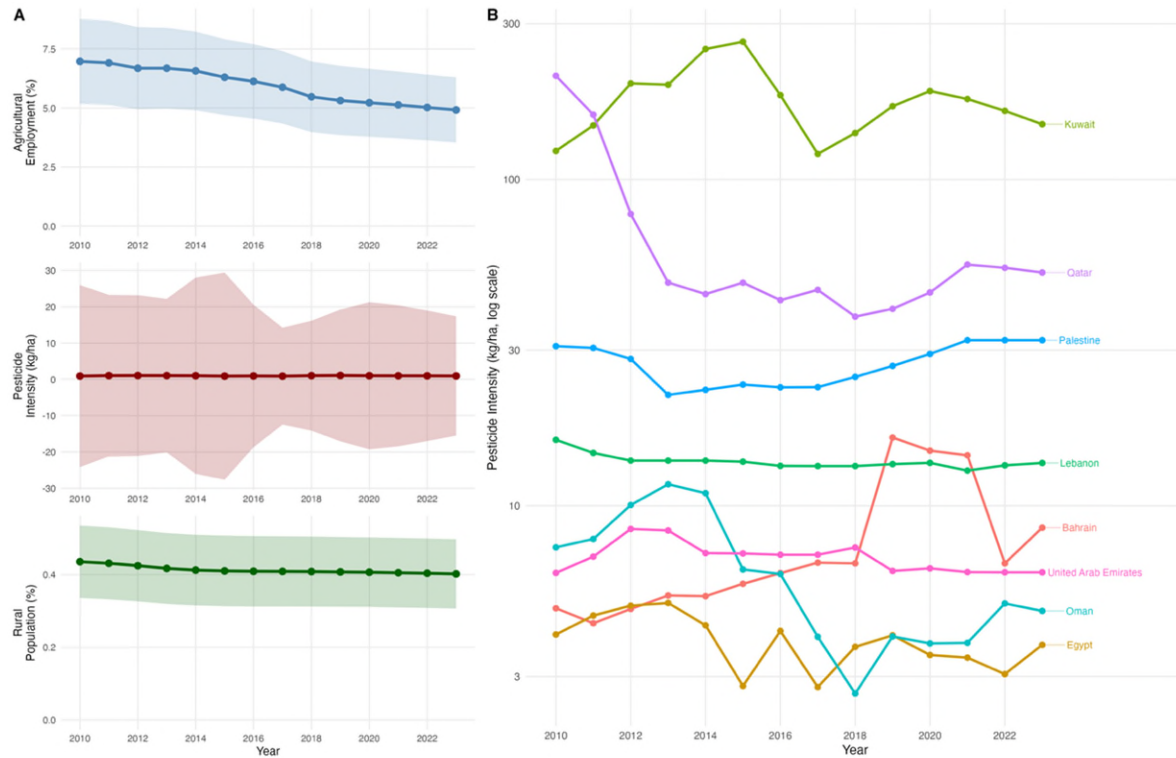


Figure 1. Temporal trends in pesticide exposure drivers across MENA region, 2010-2023. Panel A displays MENA aggregate temporal dynamics for three key exposure determinants: agricultural employment as percentage of total workforce (top), pesticide application intensity in kg per hectare (middle), and rural population as percentage of total population (bottom). Shaded regions represent 95% confidence intervals calculated from inter-country variability. Panel B shows country-specific pesticide application intensity trajectories for the eight countries with highest mean intensity over the study period. Y-axis uses logarithmic scale to accommodate the wide range of application rates across countries.

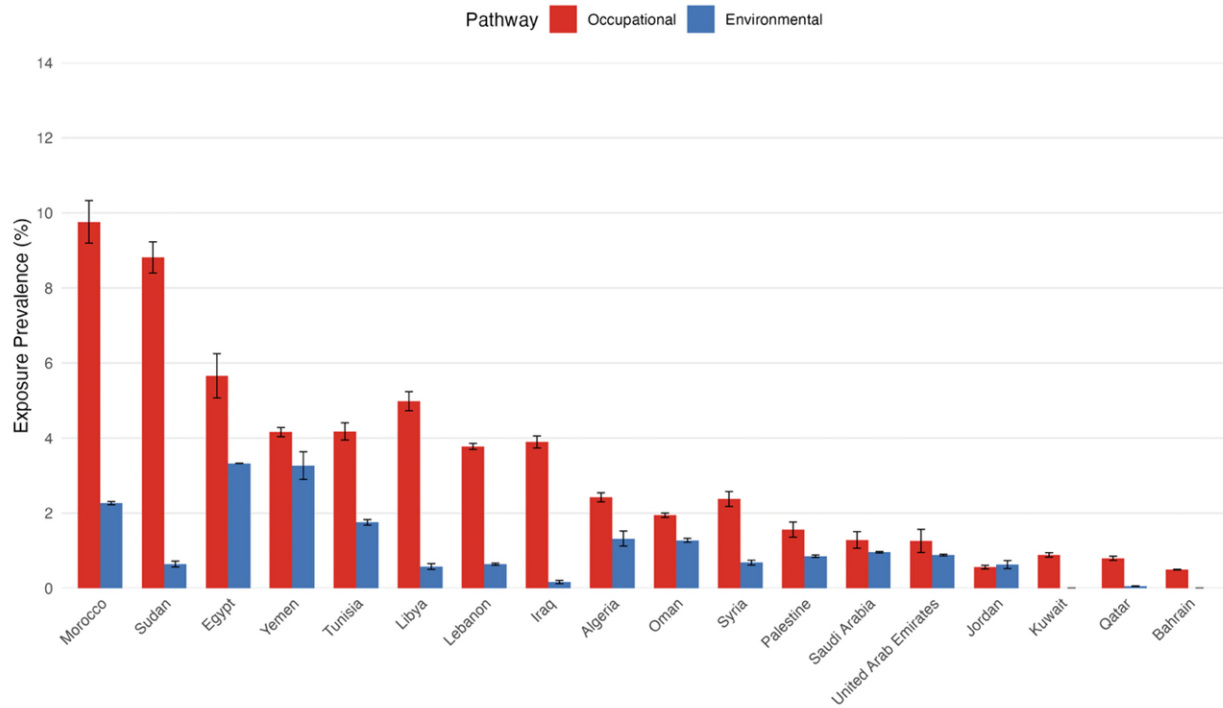


Figure 2. Estimated Pesticide Exposure Prevalence by Pathway in MENA Countries. Grouped bar chart displaying mean exposure prevalence (2010–2023) for occupational (red) and environmental (blue) pathways. Error bars = ± 1 SE. Occupational: 80% of agricultural workforce. Environmental: rural population % $\times \min(0.58, \text{pesticide kg/ha} \div 10)$, where 0.58 = fraction of rural residents with crops within 500m (Ward et al., 2006). Countries ranked by total exposure.

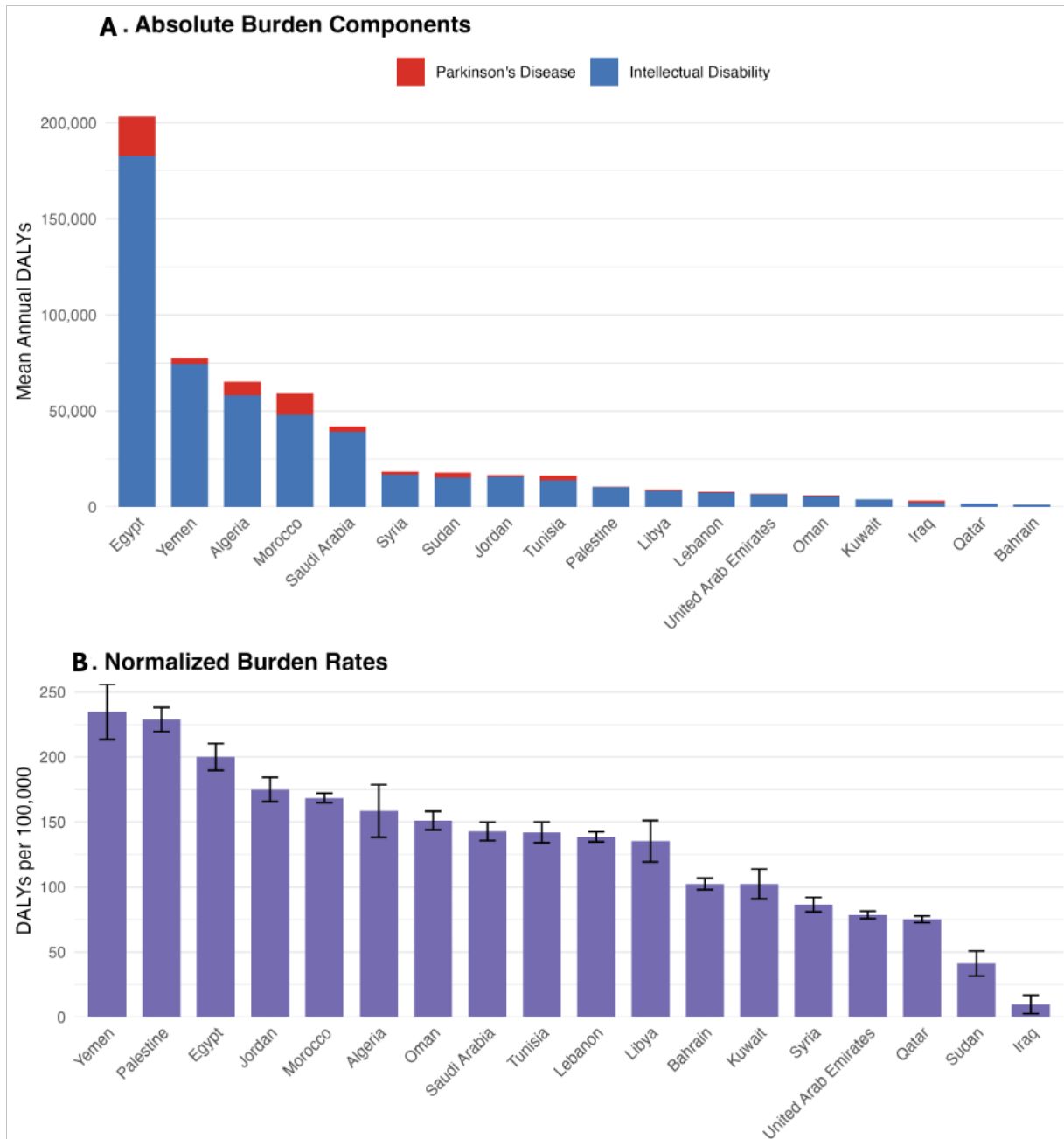


Figure 3. Pesticide-attributable neurological burden in MENA countries, 2010-2023. Panel A shows absolute burden decomposed into intellectual disability (blue) and Parkinson's disease (red) components, with countries ranked by total burden from highest to lowest. Panel B presents per-capita burden rates (DALYs per 100,000 population) with 95% confidence intervals, ranked by rate magnitude. All values represent mean annual estimates across 2010-2023.

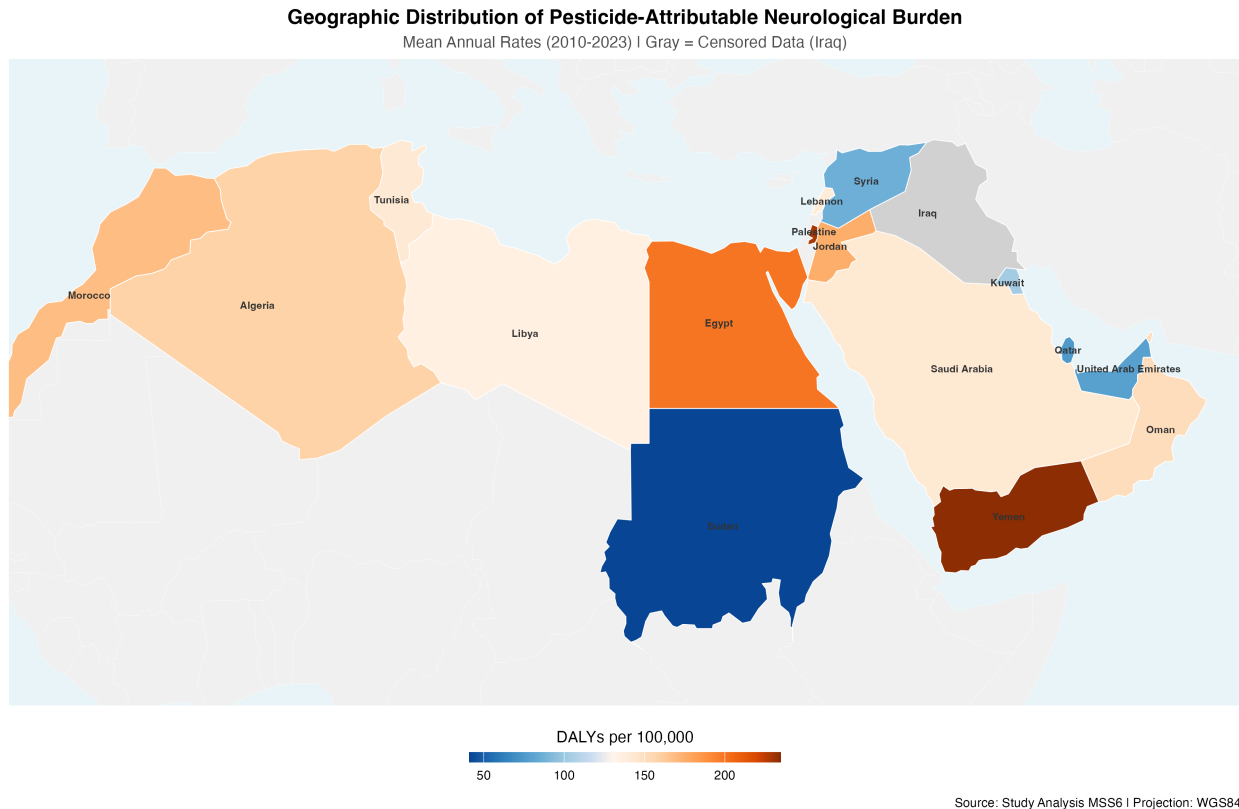


Figure 4. Geographic Distribution of Pesticide-Attributable Neurological Burden Across MENA Region, 2010-2023. Choropleth map displays mean annual burden rates (DALYs per 100,000 population) with color intensity scaled from dark blue (lowest burden) through purple (moderate) to yellow (highest burden). Iraq shown in gray indicates censored data due to pesticide application intensity falling below reference threshold (0.1 kg/ha) in 8 of 14 study years. Color scale represents population-normalized burden intensity rather than absolute DALYs to account for demographic variation across countries.

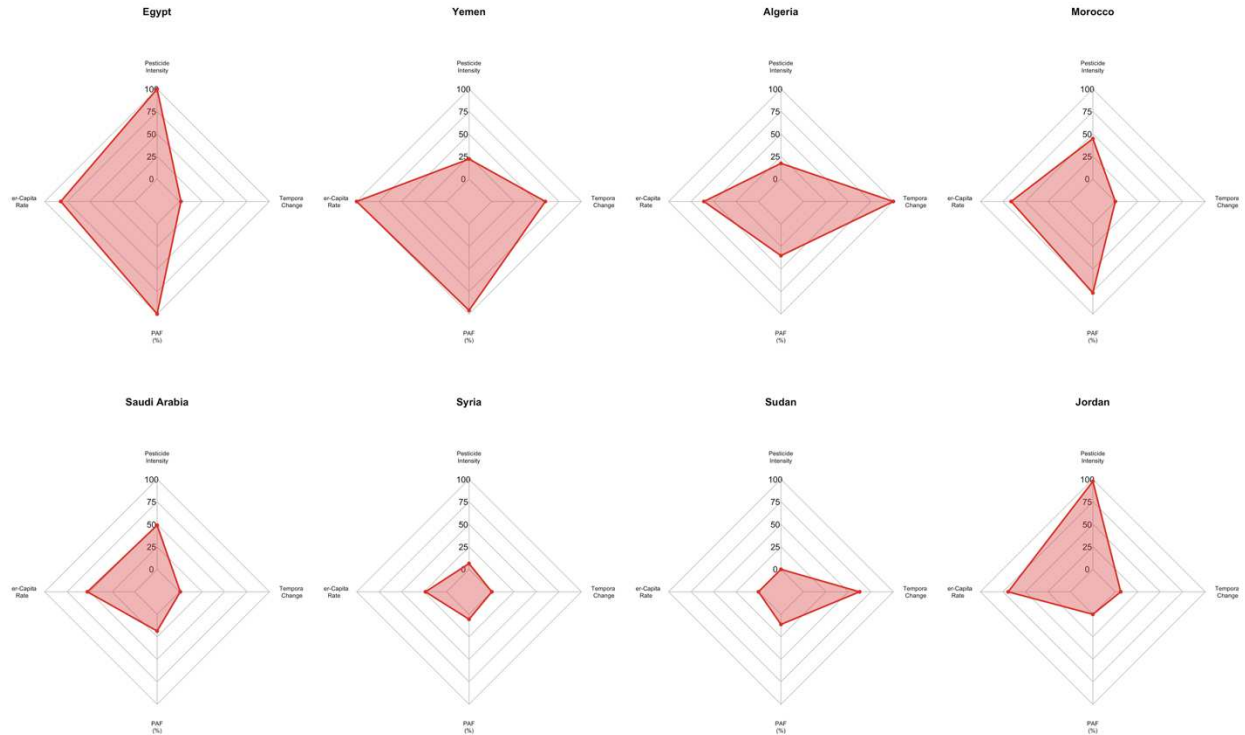


Figure 5. Multidimensional country risk profiles for pesticide-attributable neurological burden in top eight MENA countries, 2010-2023. Radar charts display normalized scores (0-100 scale) across four risk dimensions for countries ranked by mean total burden. Axes represent: (1) Pesticide Application Intensity (mean kg active ingredient per hectare agricultural land), (2) Per-Capita Burden Rate (mean DALYs per 100,000 population), (3) Population Attributable Fraction for Parkinson's disease (combined occupational and environmental exposure pathways, percentage), and (4) Temporal Burden Change (percentage change in total DALYs from 2010 to 2023). Normalization scales each dimension from 0 (minimum observed value) to 100 (maximum observed value) across all countries to enable cross-dimensional comparison. Larger polygon areas indicate higher multi-dimensional risk profiles.

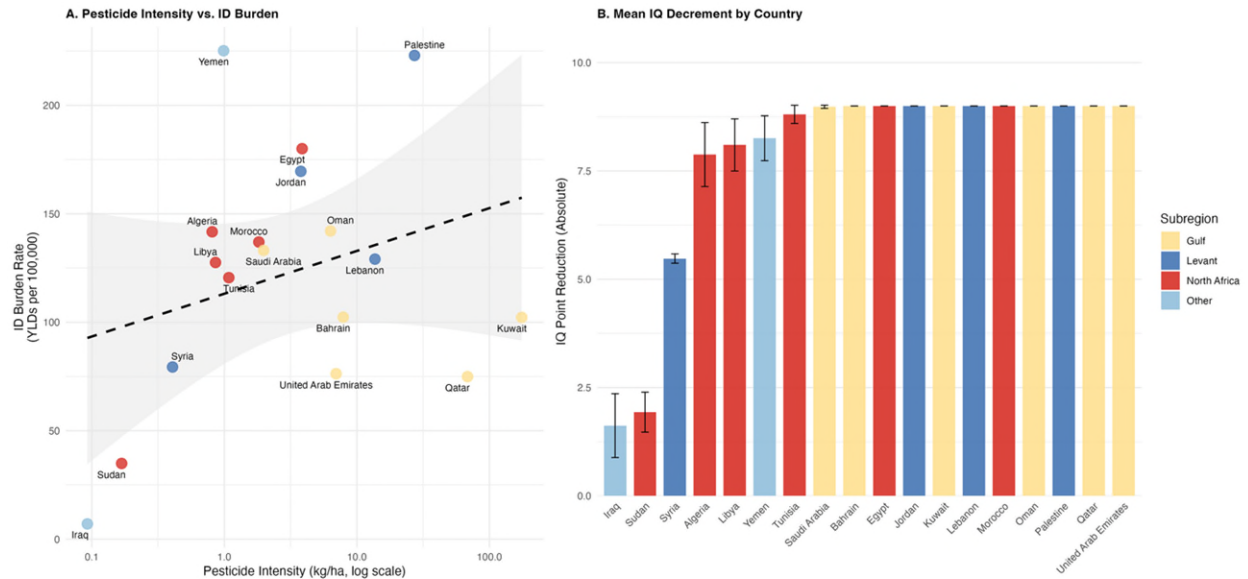


Figure 6. Dose-Response Relationships Between Pesticide Application Intensity and Neurological Burden in MENA Countries. Panel A: Scatter plot of mean pesticide application intensity (kg/ha, logarithmic scale) versus mean intellectual disability burden rate (YLDs per 100,000 population), 2010-2023. Panel B: Country-specific mean IQ decrements with 95% confidence intervals, ranked from lowest to highest. Red dashed horizontal line indicates the 9.0-point Bouchard et al. upper 95% CI threshold applied as biological plausibility cap. Points color-coded by subregion: North Africa (red), Levant (blue), Gulf (yellow), Other (light blue). Dashed trend line represents linear regression with 95% confidence interval (gray shading).

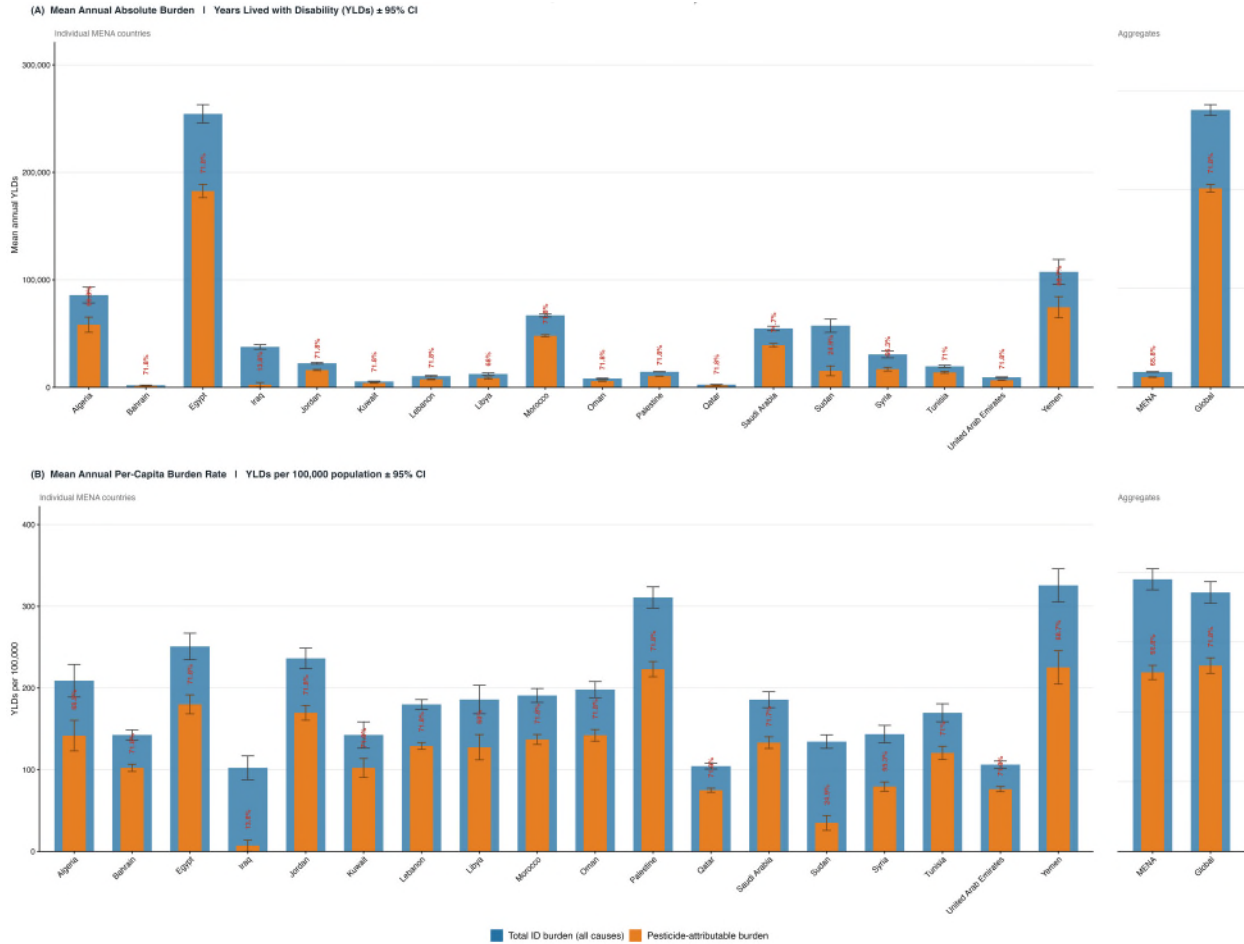


Figure 7. Pesticide-attributable intellectual disability burden compared to total intellectual disability burden from all causes in MENA and global populations, 2010–2023. Panel A shows mean annual absolute burden (years lived with disability, YLDs); Panel B shows mean annual per-capita burden rates (YLDs per 100,000 population). Orange bars represent pesticide-attributable burden; blue bars represent total burden from all causes. Error bars denote 95% confidence intervals derived from inter-annual variability ($n = 14$ years). Red percentages indicate the population attributable fraction (PAF). Individual MENA countries and regional/global aggregates are displayed on independent y-axis scales. Total ID burden estimated by back-calculation from attributable burden using country-specific PAFs. MENA aggregates 18 countries (~450 million people).

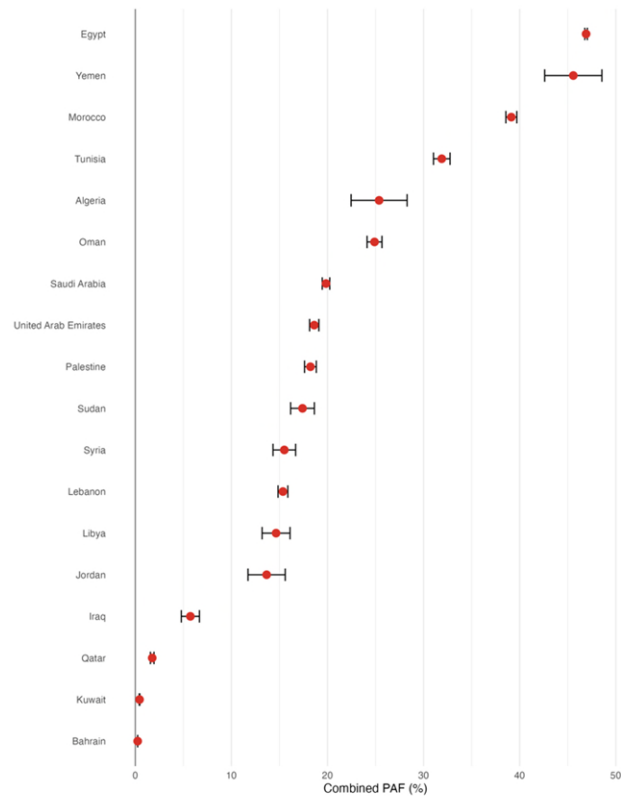


Figure 8. Forest plot of country-specific combined population attributable fractions for Parkinson's disease, 2010-2023 average. Horizontal lines represent 95% confidence intervals for combined PAF; points indicate mean estimates. Countries ranked from lowest (top) to highest (bottom) PAF. Combined PAF calculated using multiplicative formula for competing exposures: $PAF_{combined} = 1 - (1 - PAF_{occupational})(1 - PAF_{environmental})$. Occupational PAF based on $RR = 1.5$ (95% CI: 1.3-1.7) from meta-analyses of farmworker studies; environmental PAF based on $RR = 1.25$ (95% CI: 1.15-1.35) from residential proximity studies. Confidence intervals derived by propagating RR uncertainty through PAF calculations using parameter substitution method across 14 annual observations.

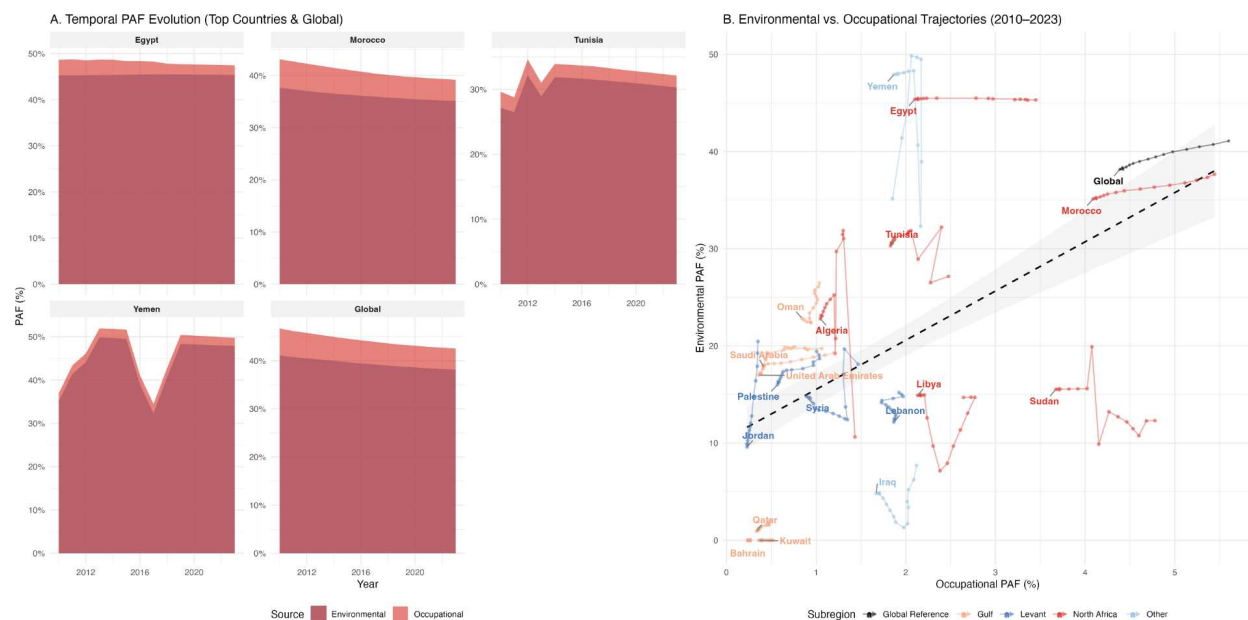


Figure 9. Population Attributable Fraction Decomposition by Exposure Pathway in MENA Countries, 2010-2023. Panel A: Temporal evolution of PAF components for four highest- burden countries (Egypt, Morocco, Tunisia, Yemen) plus Global reference. Stacked area charts display environmental (dark red, bottom) and occupational (light red, top) pathway contributions. Panel B: Relationship between environmental and occupational PAF across 252 country-year observations (18 countries $\times$ 14 years). Each point represents one country-year; colors denote subregions (North Africa: red, Levant: blue, Gulf: yellow, Other: light blue). Dashed black line shows linear regression with 95% confidence interval. Global reference trajectory (black dashed line with points) provided for comparison in Panel B.

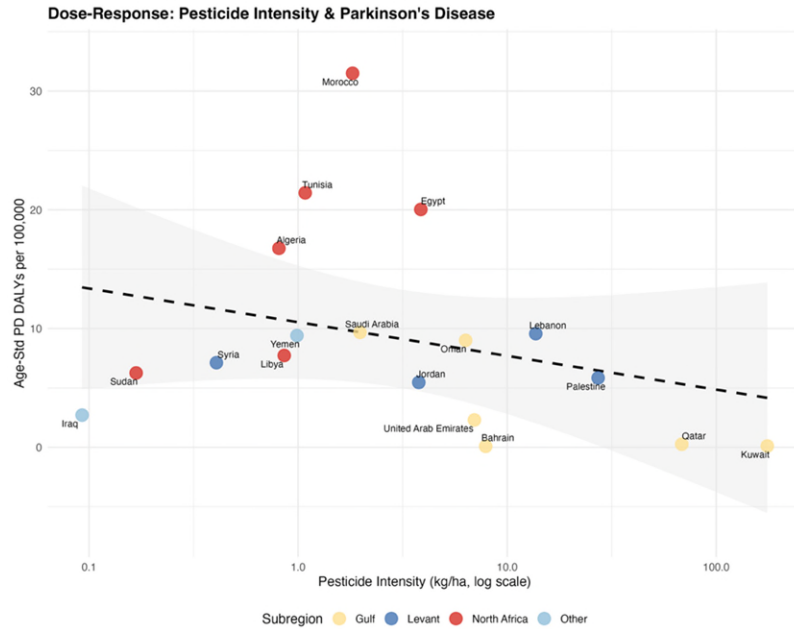


Figure 10. Dose-Response Relationship Between Pesticide Application Intensity and Age-Standardized Parkinson's Disease Burden in MENA Countries, 2010-2023. Scatter plot displays mean pesticide intensity (kg/ha, logarithmic scale) versus mean age- standardized PD burden rate (DALYs per 100,000 population). Each point represents one country's 14-year average, color-coded by subregion (North Africa: red, Levant: blue, Gulf: yellow, Other: light blue). Dashed trend line shows linear regression with 95% confidence interval (gray shading).

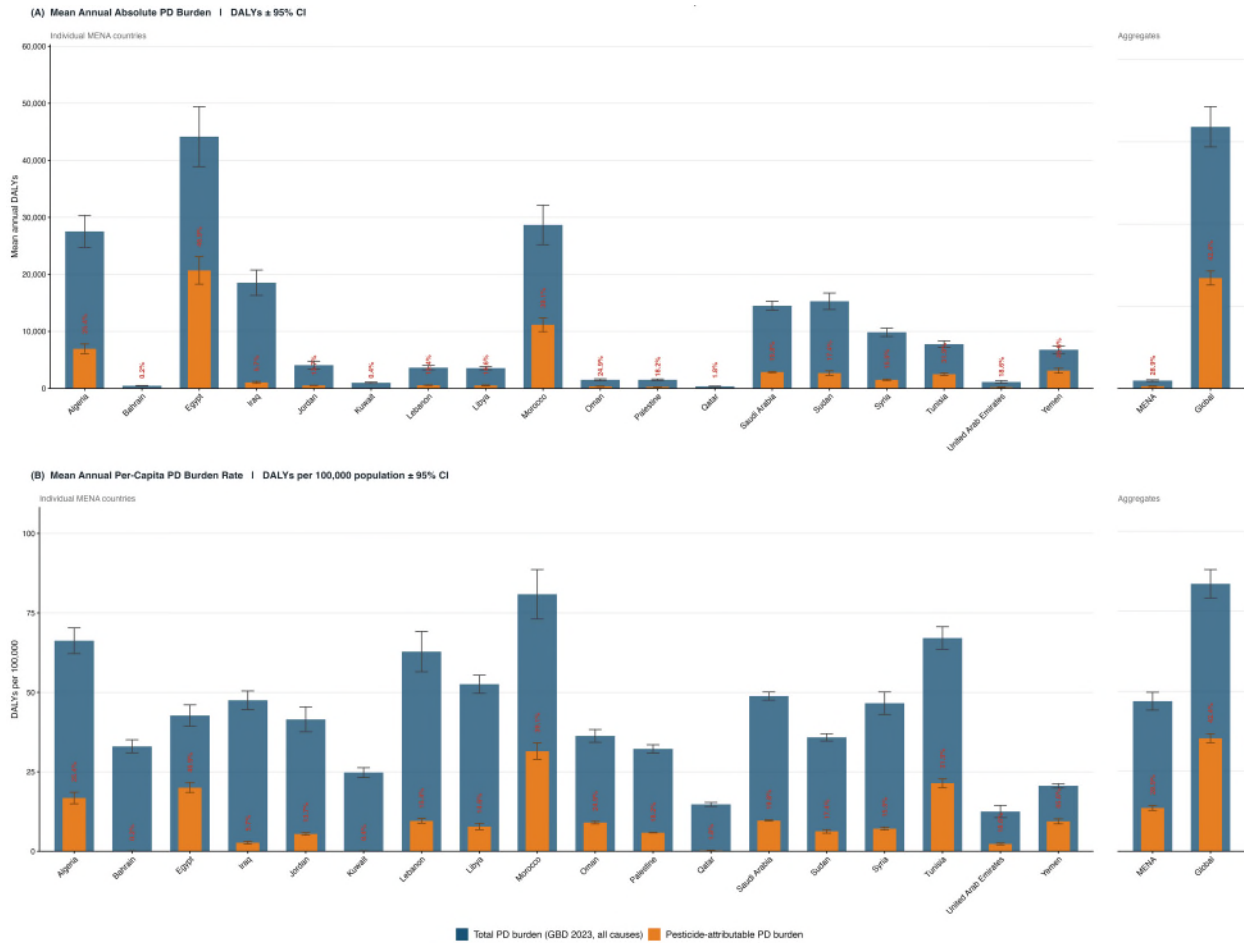


Figure 11. Pesticide-attributable Parkinson's disease burden compared to total Parkinson's disease burden from all causes in MENA and global populations, 2010–2023. Panel A shows mean annual absolute burden (disability-adjusted life years, DALYs); Panel B shows mean annual per-capita burden rates (DALYs per 100,000 population). Orange bars represent pesticide-attributable burden; blue bars represent total burden from all causes sourced from GBD Study 2023. Error bars denote 95% confidence intervals derived from inter-annual variability ($n = 14$ years). Red percentages indicate the population attributable fraction (PAF). Individual MENA countries and regional/global aggregates are displayed on independent y-axis scales. MENA aggregates 18 countries (~450 million people).

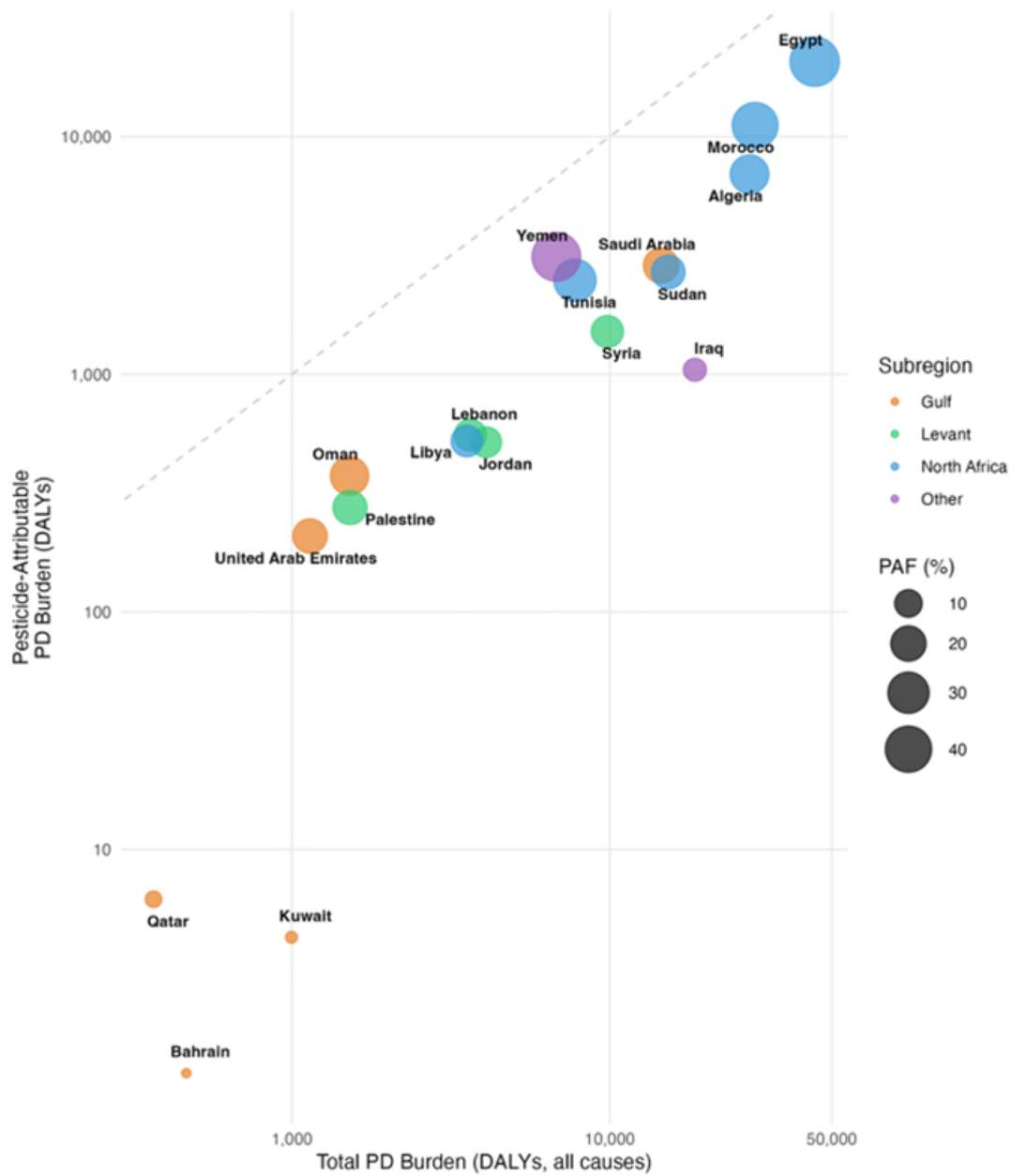


Figure 12. The relationship between total Parkinson's disease burden from all causes (x-axis) and pesticide-attributable PD burden (y-axis) on log-log scale in MENA countries, 2010-2023. Bubble size indicates population attributable fraction (PAF) percentage. Dashed line represents the 100% attribution threshold ($y=x$); countries plotting below this line have pesticide PAFs less than 100%.

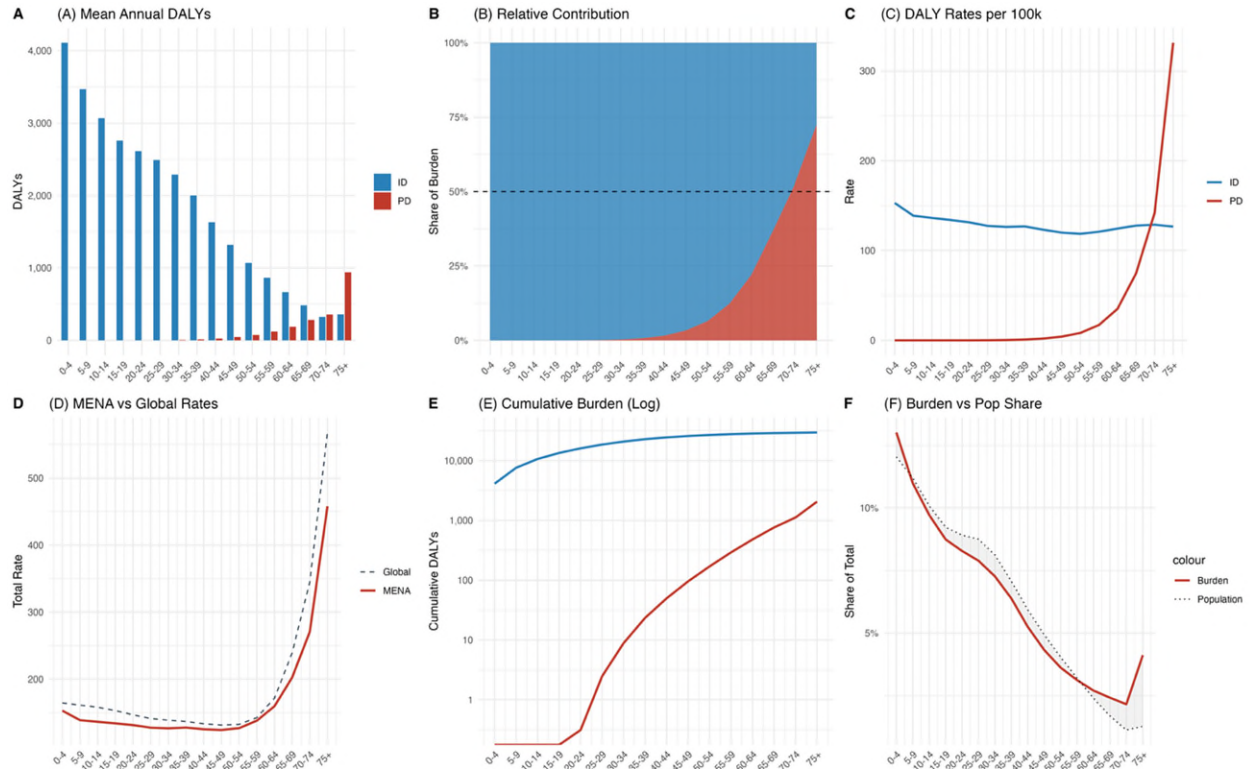


Figure 13. Neurological burden of pesticide exposure across the life-course in MENA agricultural communities, 2010–2023. (A) Mean annual absolute burden (DALYs) by five-year age group, averaged across 18 MENA countries and 14 study years (2010–2023). (B) Relative contribution of each pathway as a percentage of the age-group-specific total burden; the dashed horizontal line at 50% demarcates equal pathway contribution. (C) Age-specific DALY rates per 100,000 population by pathway component. (D) Total age-specific DALY rates per 100,000 for the MENA region (solid red line) versus global estimates (dashed dark line). (E) Cumulative life-course burden expressed as the running total of mean annual DALYs by pathway displayed on a $\log_{10}$ scale to enable simultaneous visualisation of the ID trajectory (dominant across the first five decades) and the PD trajectory (dominant from the seventh decade onward). (F) Age-specific burden share (percentage of total MENA DALYs attributed to each age group) versus population share (percentage of total MENA population in each age group).

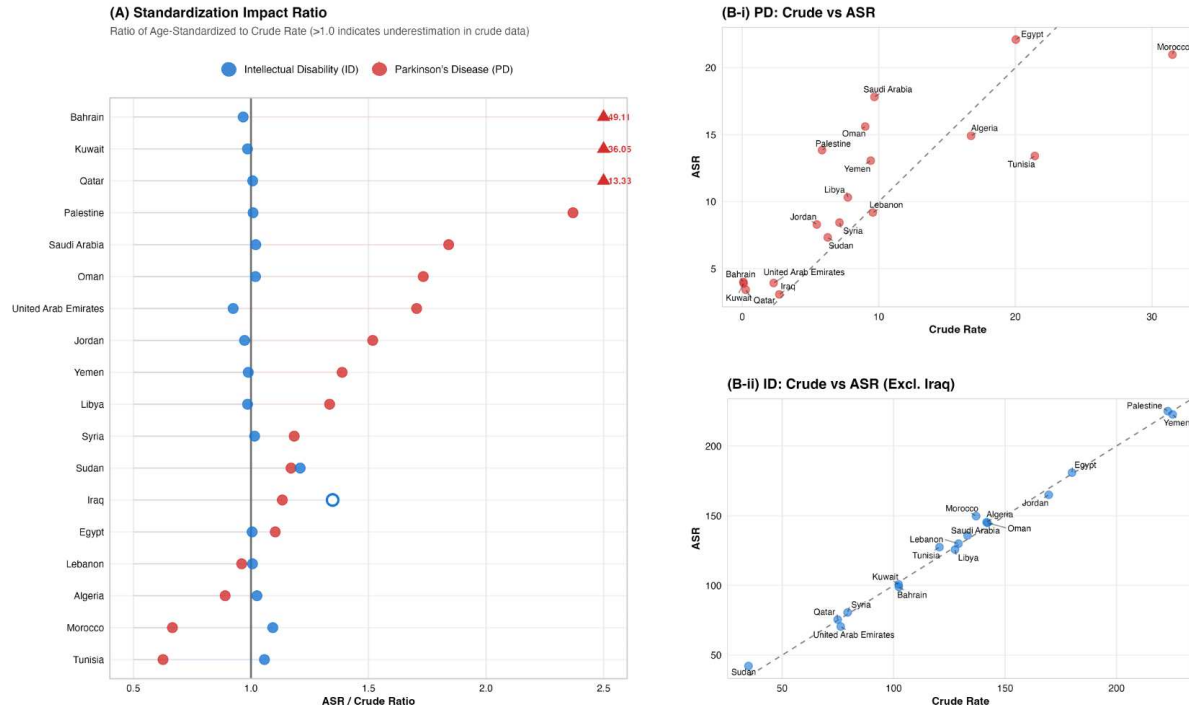


Figure 14. Impact of age standardization on pesticide-attributable burden estimates for Parkinson's disease (PD) and intellectual disability (ID) across MENA countries, mean values 2010–2023. (A) Ratio of age-standardized DALY rates (ASR) to crude DALY rates by country for PD (red circles) and ID (blue circles); the vertical line at 1.0 indicates no standardization effect, ratios above 1.0 indicate that crude rates underestimate true burden relative to the WHO World Standard Population, and out-of-range values are shown as triangles at the axis boundary with their true ratio labelled. The hollow circle for Iraq (ID) reflects a data anomaly in the source crude rate and should be interpreted with caution. (B-i) Scatter plot of crude versus age-standardized PD DALY rates per 100,000 population; (B-ii) scatter plot of crude versus age-standardized ID DALY rates per 100,000 population (Iraq excluded); in both panels the dashed diagonal represents perfect concordance, and country labels identify all 18 MENA countries.

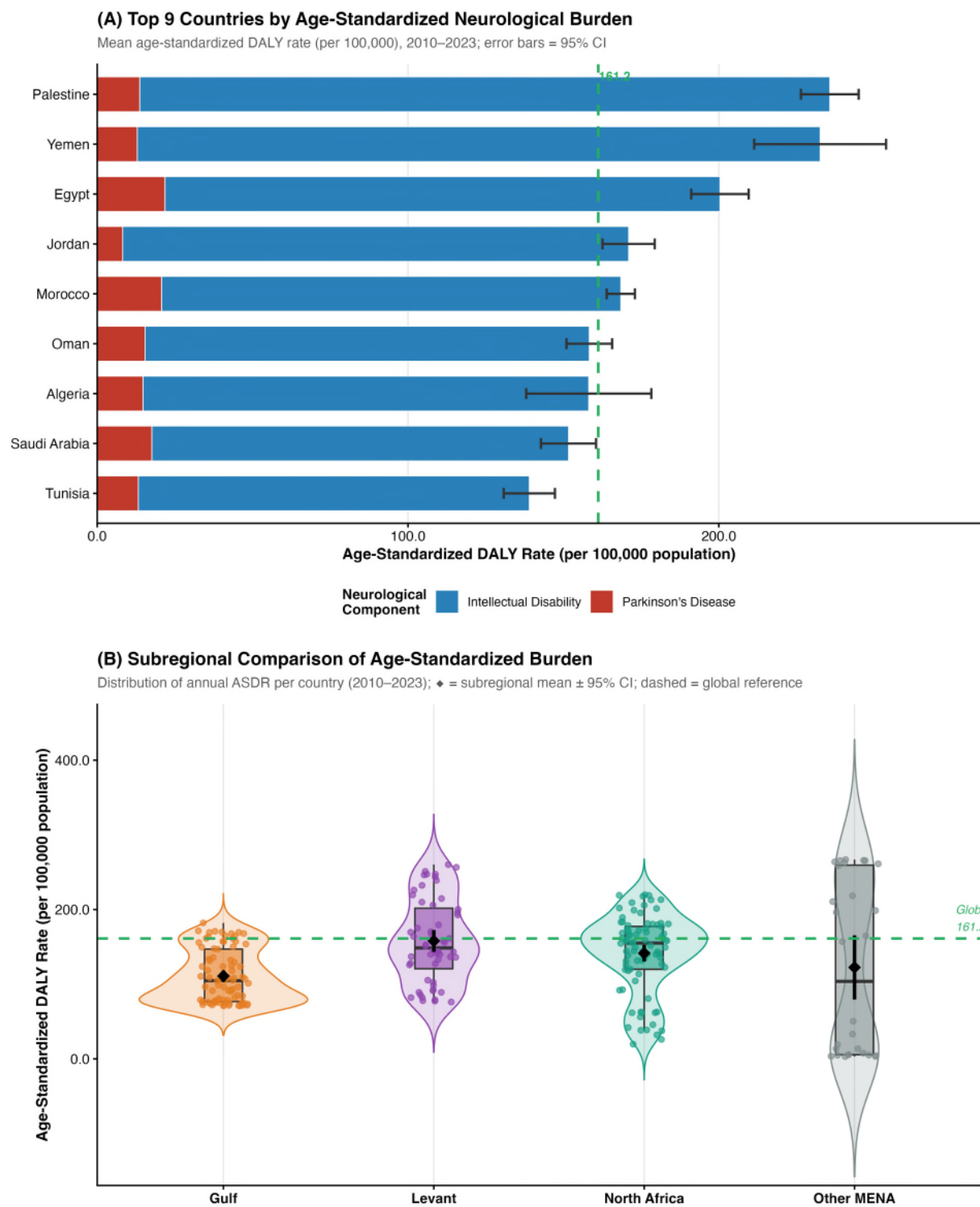


Figure 15. Top 9 Countries by Age-Standardized Pesticide-Attributable Neurological Burden Compared to the Global Reference (2010–2023). (A) Horizontal stacked bar chart showing the nine MENA countries with the highest mean age-standardized DALY rate (per 100,000 population) attributable to pesticide exposure, averaged across 2010–2023. Bars are segmented by neurological component: intellectual disability (blue) and Parkinson's disease (red); error bars represent 95% confidence intervals; the dashed green vertical line indicates the global mean age-

standardized DALY rate for reference. (B) Violin plots with embedded box plots showing the distribution of annual country-level age-standardized DALY rates across the four MENA subregions (2010–2023); individual country-year observations are shown as jittered points; the diamond symbol (◆) denotes the subregional mean $\pm$ 95% CI; the dashed green horizontal line indicates the global reference rate.

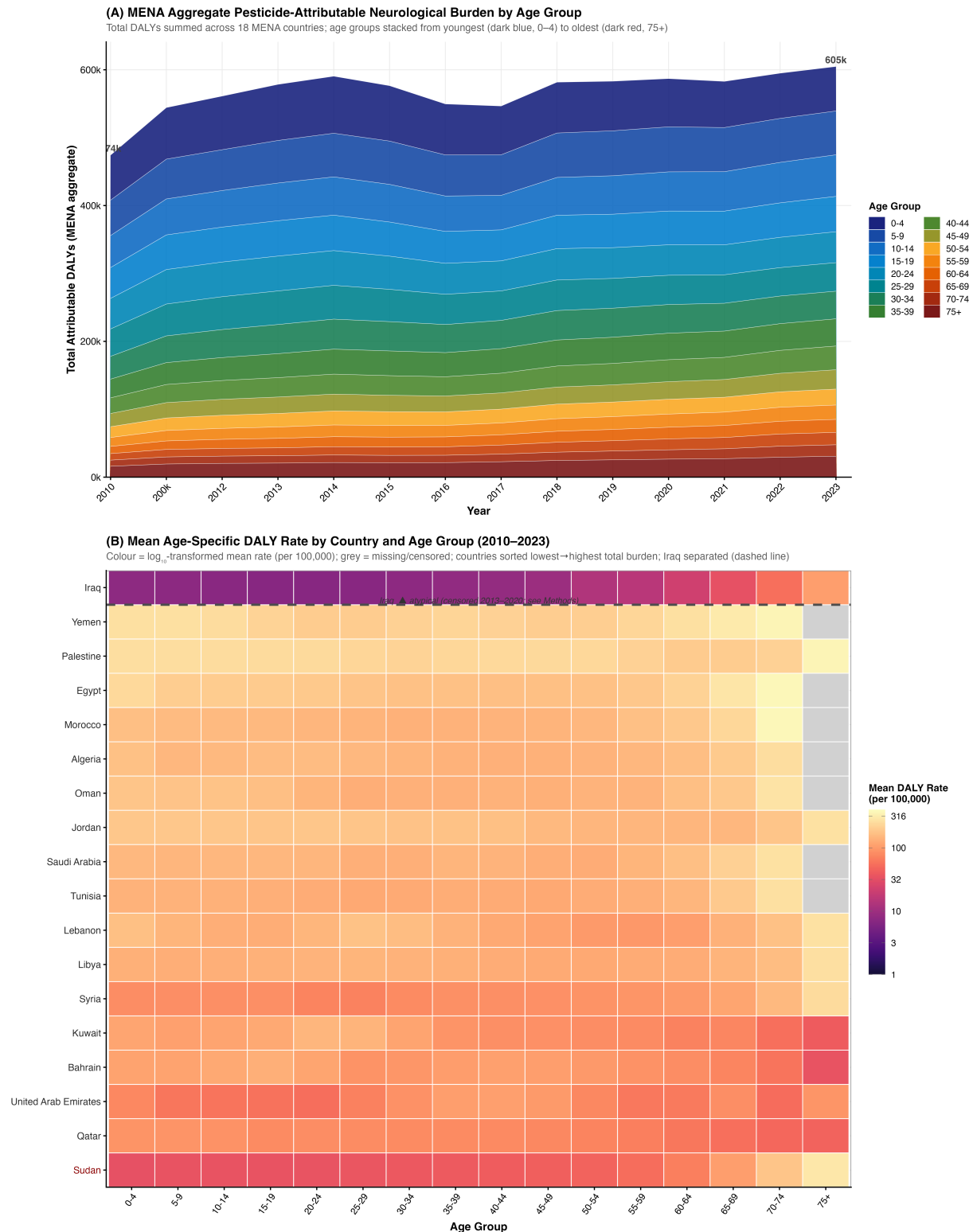
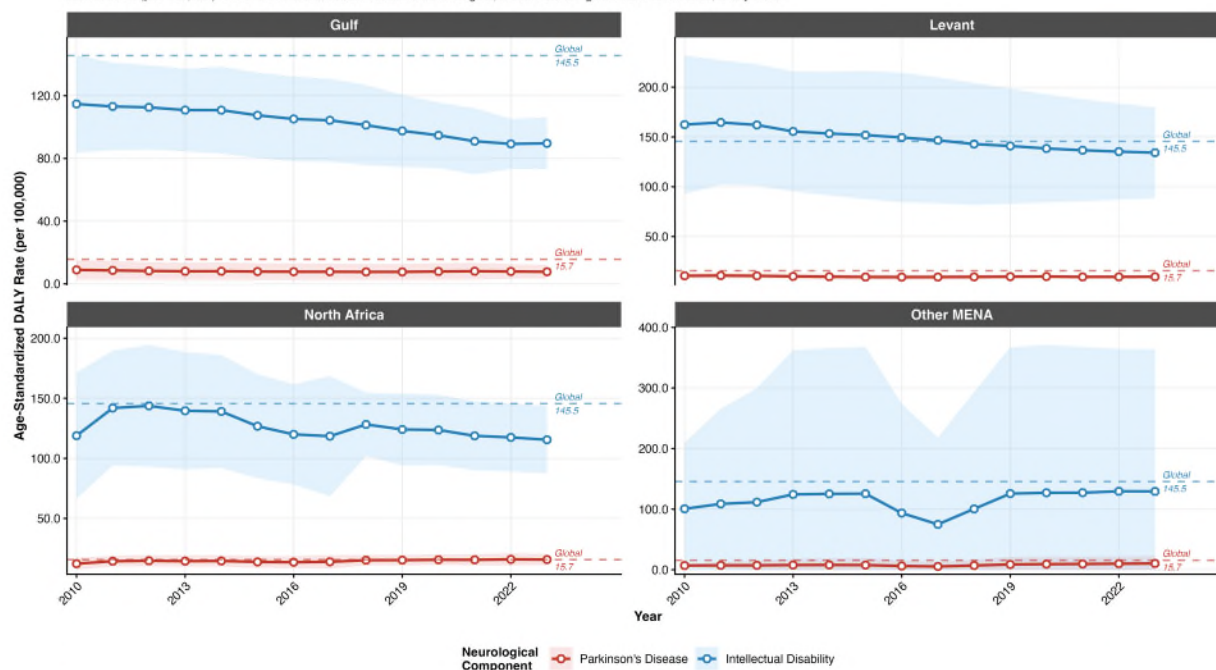


Figure 16. Temporal Trends in Age-Standardized Pesticide-Attributable Neurological Burden Across MENA Countries, 2010–2023. (A) Stacked area chart showing MENA aggregate pesticide-attributable neurological DALYs decomposed by age group over time, summed across all 18 MENA countries. Each band represents one five-year age group; colour gradient progresses from dark blue (youngest: 0–4 years) through green and orange to dark red (oldest: 75+ years). Annual totals at 2010 and 2023 are annotated. (B) Heatmap displaying mean age-specific

DALY rates (per 100,000 population) averaged across 2010–2023, by country (rows, sorted lowest to highest total burden) and five-year age group (columns). Fill colour represents $\log_{10}$ -transformed rates using the magma colour scale: dark purple (~ 1 per 100,000) to bright yellow (> 300 per 100,000); grey tiles indicate missing or censored values. Iraq is displayed separately at the top of the heatmap (above the dashed line) due to systematic data censoring during 2013–2020 when pesticide intensity fell below the reference threshold.

(A) Temporal Trends in Pesticide-Attributable Burden by Subregion with Uncertainty Quantification

Mean ASDR (per 100,000) $\pm$ 95% CI across countries within each subregion; dashed lines = global mean reference; free y-axes



Individual country ASDR trajectories (per 100,000): dashed green line = global mean; Iraq dashed/x markers = data anomaly (censored 2013–2020); y-axis free per subregion

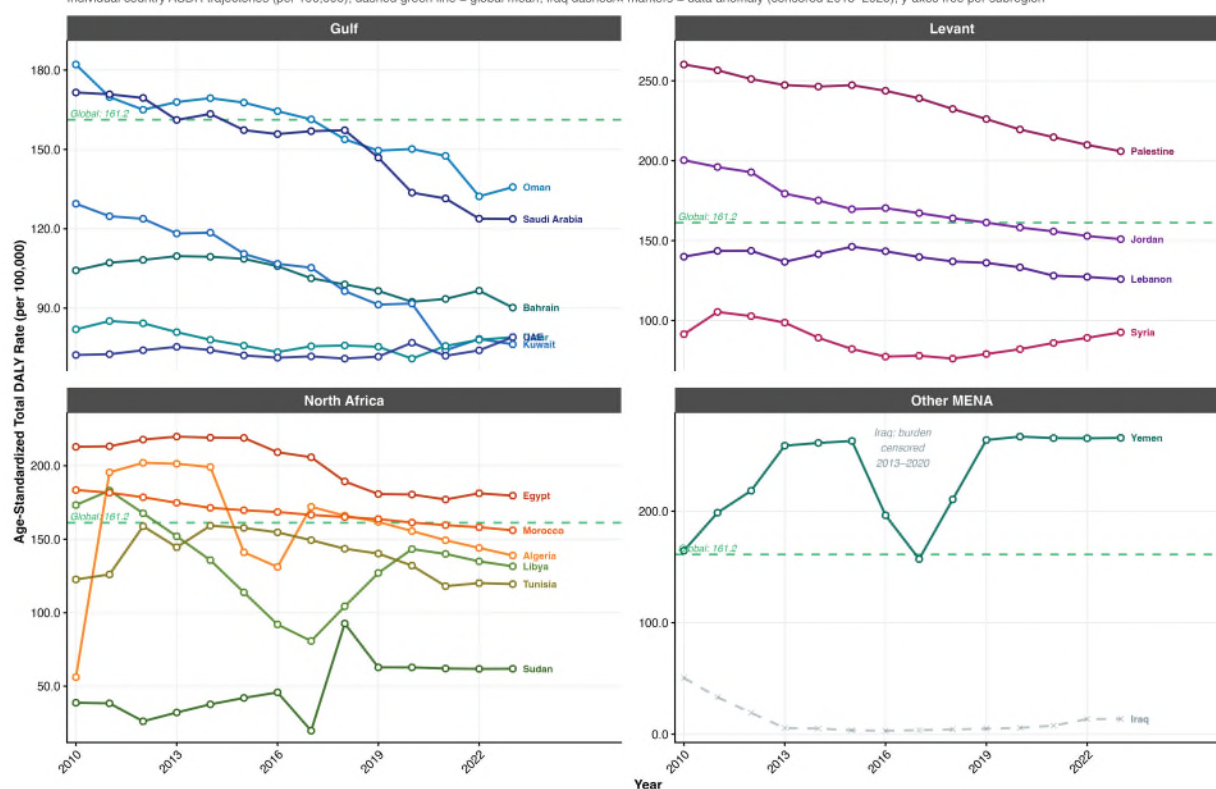


Figure 17. Temporal Trends in Age-Standardized Pesticide-Attributable Neurological Burden Across MENA Countries, 2010–2023. (A) Subregional temporal trends in age-standardized DALY rates with uncertainty quantification. Mean age-standardized DALY rates (per 100,000 population) for Parkinson's disease (red) and

intellectual disability (blue) are plotted over the 14-year study period for four MENA subregions (Gulf, Levant, North Africa, Other MENA), with shaded bands representing 95% confidence intervals computed across countries within each subregion for each year. Dashed lines indicate global mean reference rates for each neurological component. Y-axes are scaled independently per subregion. (B) Country-specific temporal trajectories of total age-standardized DALY rates (per 100,000), stratified by geographic subregion across four faceted panels. Each line represents one country across 2010–2023. The dashed green horizontal line in each panel indicates the global mean total ASDR (161.2 per 100,000) for reference. Iraq is displayed as a dashed line with cross markers to flag systematic data censoring during 2013–2020 when pesticide application intensity fell below the reference threshold.

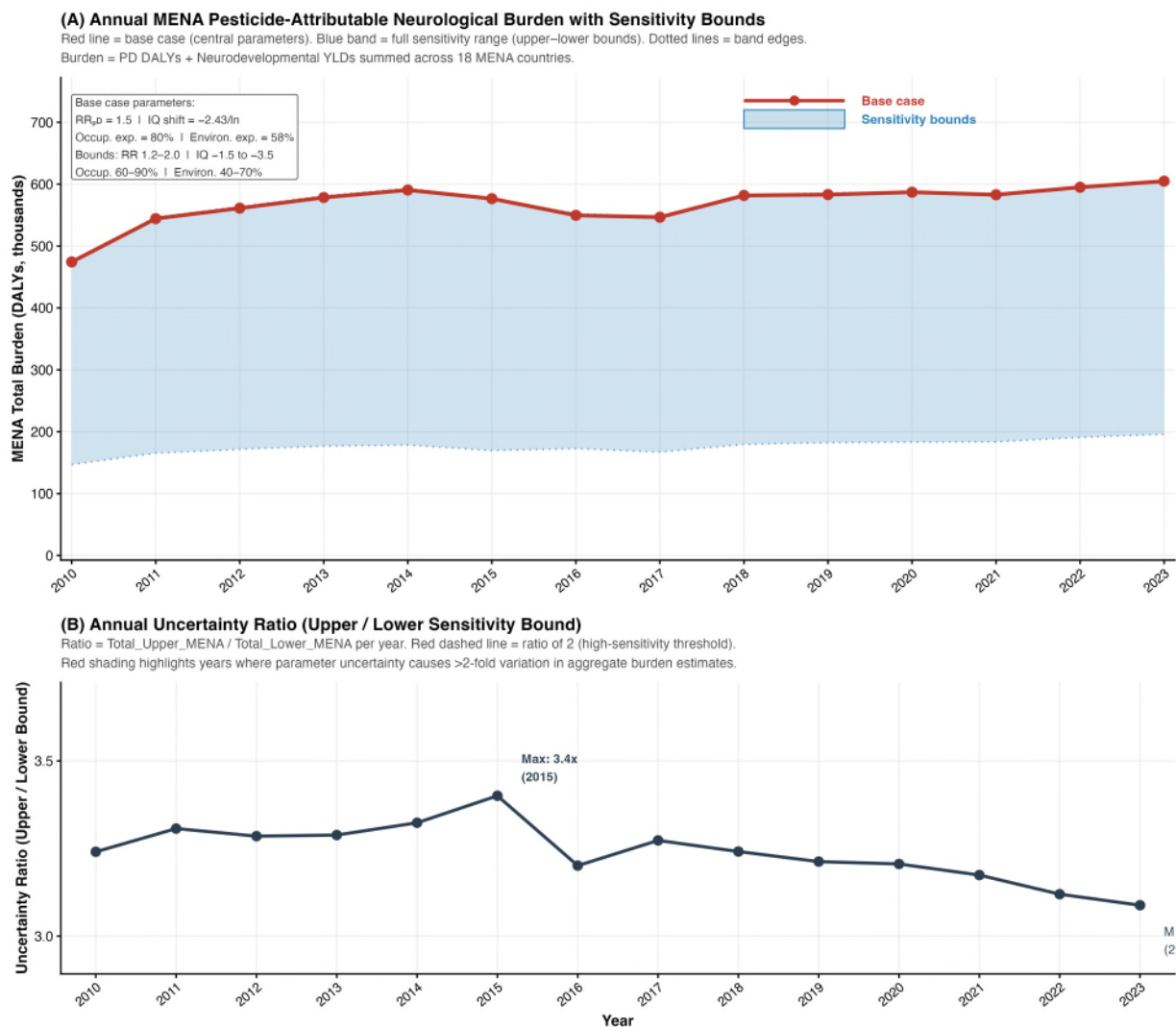


FIGURE 18: Annual MENA Pesticide-Attributable Neurological Burden with Uncertainty Quantification for Sensitivity Analysis, 2010–2023. (A) Time series of total pesticide-attributable neurological burden (PD DALYs + neurodevelopmental YLDs) aggregated across 18 MENA countries, showing the base case estimate (red line with points) and the full sensitivity range (blue shaded band). The base case uses central parameter values: $RR_{PD} = 1.5$, IQ-shift coefficient = -2.43 per $\ln$ unit, occupational exposure = 80% of agricultural workers, and environmental exposure = 58% of rural residents. The sensitivity band encompasses extreme parameter combinations (RR_{PD} 1.2–2.0, IQ shift -1.5 to -3.5 , occupational exposure 60–90%, environmental exposure 40–70%). (B) Annual uncertainty ratio (upper bound / lower bound), quantifying the fold-difference in aggregate MENA burden estimates across the full parameter space; the dashed red line marks a ratio of 2, above which estimates are considered highly sensitive to parameter uncertainty.

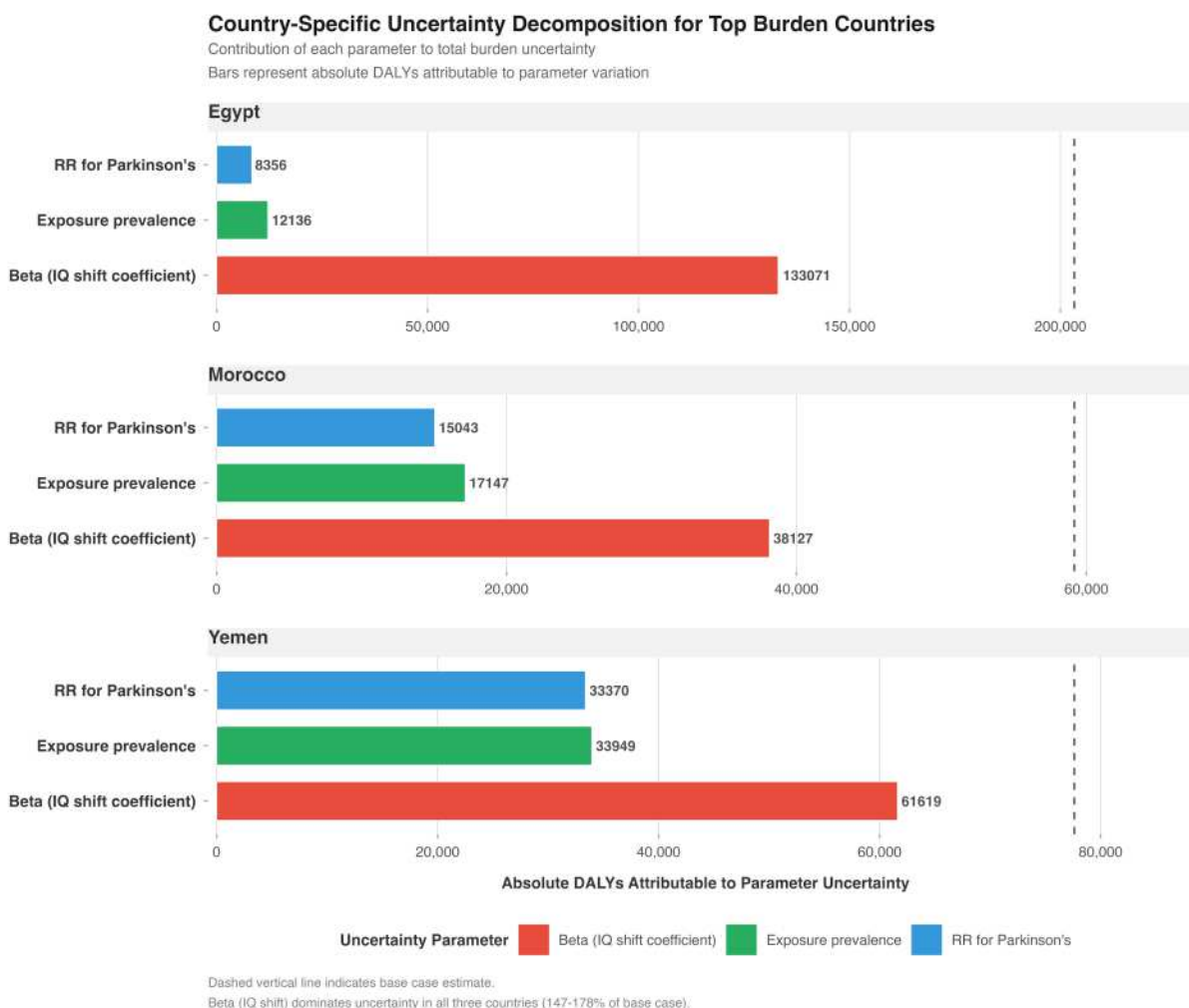


Figure 19. Country-specific uncertainty decomposition for top pesticide-attributable burden countries. Horizontal stacked bar charts display the absolute contribution of three key parameters to total uncertainty in pesticide-attributable neurological burden estimates for Egypt, Morocco, and Yemen. Bars are disaggregated by uncertainty parameter: beta coefficient (IQ shift coefficient, red), exposure prevalence assumptions (green), and relative risk for Parkinson's disease (blue). Each segment represents the absolute DALYs attributable to variation in that individual parameter, derived from sensitivity analyses across plausible epidemiological ranges. The dashed vertical line indicates the base case estimate. Note that the three parameters are varied independently and do not sum to the total uncertainty range due to interaction effects and correlation structure in the underlying exposure-response relationships.

Supplementary Files

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- [Supplementaryfiguresv2.docx](#)