Relationship Between Freshwater Harmful Algal Blooms and Neurogenerative Disease Incidence Rates in South Korea

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Research Article

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Abstract

Background: Due to anthropogenic activities and global warming, the severity and distribution of harmful algal blooms (HABs) have been increasing steadily worldwide, including in South Korea (S. Korea). Previous studies reported exposure to HABs can increase the risk of HAB-related diseases. However, very few studies examined the linkage between HABs and disease occurrence, particularly in S. Korea. The objective of this study was to evaluate the potential impact of HABs on neurodegenerative diseases (NDs), including Alzheimer's disease, Parkinson's disease, and motor neuron disease, at a population level.

Methods: Thirteen year data (2005-2017) for chlorophyll-*a* (chl-a) concentrations as a bloom-related parameter, annual numbers of NDs and population information were collected. First, the entire area of S. Korea was divided into a grid of 1-km and the population number in each 1-km grid was collected using Statistical Geographic Information Service Plus system. Cross-sectional time series data were analyzed with two statistical models, a generalized linear mixed model and a generalized linear model.

Results: The results show that there is a general trend of increasing chl-a concentration and NDs year by year. We observed positive correlations between HAB intensity and incidence rate of NDs. Particularly, HABs seem to have the most long-term carry-over effect on Parkinson's disease. Another key finding was that a 5-km radius from the HAB location was the boundary that showed most significant associations with three NDs.

Conclusions: This study provides statistical evidence that supports the potential risk of NDs from the exposures of HAB. Thus, it is recommended to monitor a broad spectrum of cyanotoxins, including neurotoxins, in the areas of bloom-affected regions in S. Korea as well as epidemiological studies in the future.

Background

Cyanobacterial harmful algal blooms (HABs) in freshwater have been intensified by eutrophication and climate change, and expanded globally (Metcalf et al., 2021). A major public health concern of HABs is that some species of cyanobacteria produce toxic metabolites, known as cyanotoxins, such as microcystin, nodularin, cylindrospermopsin, anatoxin-a, and saxitoxins, so threaten water bodies used as water resources. Cyanotoxins have neural, dermal, gastrointestinal, or/and hepatic toxicities (Lee et al., 2019; Roberts et al., 2020). Previous studies summarized that cyanotoxin exposure pathways include ingestion, inhalation, and dermal contact, and those exposures have links to animal and human health risks (Cheung et al., 2013). At a population level, a handful of studies reported HAB exposure and related health risks. Zhang et al. (2015) and Lee et al. (2019) reported a significant positive association between cyanobacterial blooms and non-alcoholic liver disease in United States (US) and South Korea, respectively. In addition, Li et al. (2011) revealed the relationship between chronic microcystin exposure and liver damage of children in China. Gorham et al. (2020) showed that using cyanobacterial bloom-affected water for a drinking water source is a significant risk factor for increased hepatocellular

carcinoma incidence rates in Ohio, US and Svirčev et al. (2014) reported a possible connection between HABs and multiple cancers, including brain cancer and primary liver cancer, in Serbia.

Compared to hepatotoxic effects, incidences of the cyanobacterial neurotoxin poisoning is less frequently documented (Metcalf et al., 2021). Certain cyanobacteria species produce neurotoxic metabolites in freshwater. Saxitoxins, anatoxin-a, and paralytic shellfish toxins are the major neurotoxins and β-methylamino-L-alanine (BMAA) is the bioactive peptide that is the most commonly reported as a risk factor for amyotrophic lateral sclerosis (ALS) (Caller et al., 2009; Torbick et al., 2018). BMAA was detected in the brain tissue of Alzheimer's disease (AD) patients in the US and Canada (Pablo et al., 2009). Humans can be exposed to these neurotoxins via various routes, such as drinking water, recreational water activities, aerosols and food (Metcalf et al., 2021; Cox et al., 2018). A previous study reported cyanobacterial neurotoxin accumulation in fish and shellfish (Metcalf et al., 2021), which can be an exposure pathways to higher organisms. Some reports concluded that the causal relationship between BMAA and ALS/PDC and BMAA is not supported by existing data (Chernoff et al., 2017). However, there has been accumulating evidence that long-term exposure to cyanotoxins is being identified as neurotoxic effects (Metcalf et al., 2021). BMAA is prevalent in aquatic environments (Metcalf et al., 2009) and also exists in terrestrial environments. One example is agricultural fields where water treatment sludge is disposed (Ai et al., 2020). Thus, there is a possibility that humans can be exposed to neurotoxins in various exposure pathways that have not been explored or imagined before, and there is an imperative need to study the impact of HABs on neurodegenerative diseases in the areas affected by HABs around the world.

The main goal of this study was to determine whether there are significant associations between HABs and neurodegenerative diseases (NDs) at a population level. For this, the current study analyzed three NDs (motor neuron disease (MND), AD, and Parkinson's disease (PD)), incidence rates in 1-km grid population in the Republic of Korea (hereafter South Korea (S. Korea)) from 2005 to 2017. In S. Korea, there are four major rivers that are critically important for water resources for the nation, but those rivers have been infested with severe blooms for recent decades (Lee et al., 2019). However, reports of potential impacts of HAB on human health are extremely limited. To our knowledge, this is the first study to investigate a potential linkage between HABs and ND rates at a human population level.

Methods

Collection of neurodegenerative diseases and bloom data

To identify the association between harmful algal blooms and NDs, chlorophyll-a (chl-a) concentration data and the annual number of NDs for an administrative unit ('gu' or 'gun') in S. Korea were used. Since the observed sites where chl-a concentrations were measured were located along the rivers and lakes, the administrative units were not accurately matched geographically. Thus, gridded population was used to solve this problem, which are estimates of the population in a grid cell derived with a geo-statistical model

using census or small area population counts and a number of other spatial datasets (Thomson et al., 2020).

For bloom data, chl-a concentrations from 939 locations were obtained from the Water Information System at the Korean Ministry of the Environment. Since monitoring of cyanotoxins was limited and has not been conducted on a regular basis, chl-a concentration was used as a bloom intensity indicator; the chl-a data are the only available bloom parameter covering the entire areas along the rivers and lakes during the study period from 2005 to 2017. Annual average chl-a concentrations per each location were used for analysis. A Korean governmental agency conducts monitoring of cyanobacterial cell counts, geosmin, and chl-a concentrations during HAB seasons. Measurements of BMAA, anatoxins, or saxitoxin are rarely conducted and data are not available. Therefore, in this study, chl-a concentration was used as a bloom indicator.

Conversion to gridded population

In order to map the annual HAB and ND data, the longitude and latitude information was collected for all 939 chl-a monitoring locations, and then the data were converted into geographical information system using QGIS software (version 3.22.2, https://qgis.org/en/site/). The entire area of S. Korea was divided into a grid of 1 km and then 127,595 points of the grid were generated. Next, the 939 observed locations were mapped onto the entire grid points. If two or more observation locations of chl-a correspond to one grid, the median value of chl-a concentration was used, and then mapped it onto the grid.

As a next step, the population number in each 1-km grid was collected using the SGIS (Statistical Geographic Information Service) Plus (https://sgis.kostat.go.kr) system. SGIS Plus is a location-based open service platform linked and fused with public and private data, and census data of population, households, houses, and businesses owned by Statistics Korea (Korean Bureau of Census). SGIS Plus provides a variety of statistical data according to the size of grids. The smallest size of the grid is 100 m, and the largest one is 100 km. Numbers of total population and numbers of over 65 year old were extracted for every 1-km grid from the entire areas of S. Korea. In Fig. 1, red dots represent all observed locations of chl-a concentration, and grey lines are 1-km grids. For the surrounding areas in Seoul, the capital, the 1-km grids are not distinguishable due to its highly dense population. Thus, it was enlarged for displaying better granularity.

Figure 2 depicts more detailed information on the Seoul area. In Fig. 2, panel (a) illustrates the number of people in the 1-km grid in Seoul. The darker the color is, the larger the number of populations in the area is. Panel (b) represents the observed location of chl-a concentration measured. It shows that chl-a concentrations were monitored along the rivers and streams. Panel (c) overlays gridded population and chl-a concentration observed locations. A benefit of using 1-km gridded population is its scalability: we can easily extend the grid size by aggregating the grids into 3-km or 5-km grids, and then match each extended grid with observed chl-a concentration data.

Cross-sectional time series data

After collecting chl-a concentration data over 13 years (from 2005 to 2017), we matched the gridded population to these observed years. However, SGIS Plus does not provide data every year. Statistics Korea conducted the Census every five years until 2015. Therefore, gridded population data in 2005, 2010, and 2015 were used. In 2015, Statistics Korea performed a register-based Census, and census data have been generated every year since then. Thus, we could have the gridded population data in 2005, 2010, 2015, 2016, and 2017 based on the Censuses. To match chl-a concentration data for those 13 years to irregularly observed gridded population, we had to expand the population data to 13 years. Thus, we utilized an interpolation method of missing values in time series by connecting successive non-missing input values with spline method (De Boor, 1978). Finally, we had population estimates for these missing years of 2006, 2007, 2008, 2009, 2011, 2012, 2013, and 2014.

In this study, three NDs were considered; MND, AD, and PD. The ICD-10-CM diagnosis codes were G12.2 for MND, G12.21 for ALS, G30.0 for AD, and G20 for PD. The annual numbers of patients of the three diseases from the National Health Insurance Service were collected and the data were rearranged according to the administrative units of the district. In S. Korea, a unit of district-level has three types: "Si" as a city, "Gu" as a district in metropolitan cities only, and "Gun" as a division within provinces. The total number of administrative units is 226 and less than the total number of the 1-km grid and less than the number of chl-a observed locations (939 locations). As the differences among 1-km grid, chl-a observed locations, and the number of administrative units, we had to covert the patient number corresponding to the observed chl-a concentration location.

The number of patients for each administrative district in the 1-km grid was evenly distributed according to the populations of each grid. Let x_{it} be the number of senior patients in the i^{th} administrative unit at time t and y_{jt} be the number of ND patients in the j^{th}1 km grid at the same time t. The modified number of patient $y_{jt}$is given by in Eq. (1)

$$y_{jt} = x_{it} \times \frac{G_{jt}}{P_{it}}, i = 1,2, \ldots, 226, j = 1,2, \ldots, n_i, t = 2005, \ldots, 2017( )$$

where, $P_{it}$is the number of total populations in the i^{th} administrative unit at time t, and $G_{jt}$is the number of populations in the j^{th} 1 km grid which is one of the administrative units at time t. Figure 3 depicts the heatmaps of the modified numbers of patients in a 1-km grid. From panel (b) to (d), each panel represents the heatmap of the modified number of ND patients of MND, AD, and PD, respectively. Since, many of the population lives in the Seoul metropolitan area, about one-quarter of the population of S. Korea-we zoom in on the area. The zoom-in area can be seen in the upper right corner of each panel. Other dark-colored areas are another regional capital of S. Korea. The upper left panel (a) represents the concentration of the observed spot of chl-a. We can see that the higher concentrations are located following the four big rivers in S. Korea.

As NDs are related to old age people, the number of patient in the 1-km grid needs to be adjusted after considering the population size of older people (> 65 year old). So we performed the second modification

of the number of diseases. Eq. (2) represents the second modified number of NDs according to the older population.

$$y_{jt} = x_{it} \times \frac{1}{P65_{it}} \times \frac{G_{jt}}{P_{it}}, i = 1,2, \ldots, 226, j = 1,2, \ldots, n_i, t = 2005, \ldots, 2017 (2)$$

where, $P65_{it}$ is the number of populations over 65 in the i^{th} administrative unit at time t, the other variables are the same with Eq. (1). The first product on the right side of Eq. (2) is the corrected number of ND patients according to the number of population over 65 years in the administrative unit. The updated number was revised by multiplying the ratio of 1-km grid population and administrative unit population. The final corrected number of patients was calculated for every three ND and was used as a response variable in the statistical model.

Statistical analysis

In order to examine the relationships between the HABs and the numbers of three NDs, we had to figure out two issues first: 1) to evaluate long-lasting effects of HABs on the NDs, and 2) to confirm the spatial distance impact of HABs on the three NDs. We applied generalized linear mixed models (GLMMs) for the first issue and used generalized linear models (GLMs) for the second one. For the GLMMs, we set the log link function and the normal distribution for a random component. In addition, to identify a serial correlation that the repeated measured response variable might have, we added a one-way random effect to the model (O'Hara 2009). The main effects of HABs on the variation of NDs were considered fixed effects in the model. Let y_{jt}^{k} be the corrected number of kth ND defined in Eq. (2), where $k = 1,2, 3,$ 1 is for MNDs, 2 for ADs, and 3 for PDs and z_{jt} be the observed concentration of chl-a with the same time point and location. We modeled the number of NDs for the effects of HABs in the following:

$$\log\left(y_{jt}^{k}\right) = \beta_0 + \sum_{l=0}^{\infty} \beta_{l+1} z_{j,t-l} + u_j + \epsilon_{jt}, k = 1,2, 3, j = 1,2, \ldots, 939, t = 2005,2006, \ldots, 2017 (3)$$

where u_j is a random effect of j^{th} location and we assumed that all u_j have zero mean and the same variance σ_u^2 and each u_js is independent of each other, and ϵ_{jt} is an independently and normally distributed white noise. We could reflect the serial correlation within a location by including a random effect in the model. We performed the Hausman test to determine whether the model had to include a random effect (Hausman 1978). The null hypothesis of the test was that there is zero correlation between the fixed effects and random effects. If we did not reject the null hypothesis, the random effect model was better than the fixed effect model. Based on the results of the Hausman test, all three ND models showed that the null hypothesis did not reject all. Therefore, we could say that all three models have random effects.

For the second issue, we only utilized the 2017 data set because it is the most recent one among the complete data sets, had very few missing observations and it may best reflect the spatial effect of HABs

in the model compared to other data sets. To model the ND number response variable, and GLMs were used:

$$\log\left(y_{jr}^{k}\right) = \beta_0 + \beta_{jr} z_j + \epsilon_j, k = 1,2,3, j = 1,2,\ldots,939.$$

4

In this model, the subscript k and j are the same with Eq. (3). The subscript r represents the size of the radius. We examined the change of the effects of HABs to three ND response variables according to the radius increment by 3 km and 5 km (see Supplementary Information). When we used a 1-km grid for this purpose, many grids had no population as the locations for measuring chl-a concentrations were generally on the rivers if width of the water bodies are bigger than 1-km and very close to the rivers, lakes and strems. Thus, few people reside within those 1-km grids and those grids having the red dots on the river generate lighter blue color due to the number of lower populations (Fig. 2(c)). Therefore, we used the primary grid sizes of 3 km and 5 km, instead of 1 km, for statistical analyses.

Results

During the 13 year study period, both total and senior (> 65-year old) populations in 1-km grids increased, but senior population increased faster than the general population (Fig. 4(a) and 4(b)). The chl-a concentration trend fluctuates, but it was generally on the rise (Fig. 4(c)).

The trends of three NDs are all increasing, but the varying degrees were different (Fig. 5). The increment of AD and PD numbers was much higher compared to the total number of MND during the study period, and the increasing speed of AD numbers was the most strikingly high (> 4 times increase) during the 13-year period.

Table 1 shows the associations between HAB intensity and incidence rate of three NDs over time (e.g., MND, AD, and PD) and summarizes the estimation result of GLMMs with statistically significant coefficients. HAB_{st} represents the effect of HAB_s in the same year. HAB_{st-1} and HAB_{st-2} represent the effect of HABs one year and two years ago, respectively. In the case of MND, HABs measured in the same year were significantly correlated with the MND incidence rate. In contrast, AD incidence rate was affected by HAB intensity measured one year ago as well as that of the same year. HABs continue to affect PD incidence rate for the past three years up to the present. This result implies that HABs had the most long-term carry-over effect on PD, and this effect gradually diminished as time went by. Among the three NDs, HABs seemed to have the most long-lasting impact on PD, while MND is relatively the least affected.

Next, this study evaluated the effects of HABs on the incidence rate of the three diseases (MND, AD, PD) at different geographic distances (3 km and 5 km). Two radii based on the measurement point of chl-a concentration were applied (3 km and 5 km). The predictor is the same for each disease response model, and chl-a concentration and the response variables are the numbers of diseases for two different areas. Supplementary table 1 summarizes the estimation result of GLMs for the model Eq. (4) and their

significance. Similar patterns of statistical significance among all three diseases were observed: incidence rates at 5 km radius showed more significant associations with the HABs than 3 km.

Table 1
Results of one-way random effect model that examined the relationship between HABs and neurodegenerative diseases [a].

	Variable	Estimate	Standard Error	t	P
MND	Intercept	-11.9509	0.1051	-113.74	< .0001
	$HABs_t$	0.045745	0.0129	3.55	0.0004
Alzheimer's disease	Intercept	-9.87655	0.961	-102.77	< .0001
	$HABs_t$	0.104222	0.0182	5.73	< .0001
	$HABs_{t-1}$	0.071398	0.0181	3.94	< .0001
Parkinson's disease	Intercept	-8.53985	0.0931	-91.74	< .0001
	$HABs_t$	0.069811	0.0115	6.06	< .0001
	$HABs_{t-1}$	0.045031	0.0116	3.89	0.0001
	$HABs_{t-2}$	0.040915	0.0114	3.59	0.0003
	$HABs_{t-3}$	0.034051	0.0109	3.12	0.0018

MND: Motor neuron disease

[a] Based on the numbers of diseases in each grid's adjusted population as defined in Eq. (2).

Discussion

Freshwater HABs are a serious risk affecting environmental and public health worldwide, especially due to their ability to produce various cyanotoxins (Cheung et al., 2013; USGS 2019). Our previous study demonstrated that the distribution and severity of HAB events have increased near the major rivers for the past decades in S. Korea (Lee et al., 2019). Moreover, *Microcystis*, *Anabaena*, and *Oscillatoria* were known to be predominant in S. Korea from spring to autumn, which can produce anatoxins, saxitoxins and BMAA (Joung et al., 2016; Lee et al. 2019). Kim et al. (2018) reported saxitioxin producers measured by *sxtA* and *sxtG* genes in Han River, S. Korea. In addition, anatoxin-a was detected in several lakes (e.g. Chungju Lake, Jangsong Lake, Youngsan Lake, and Younglang Lake), ranging from 417 to 1,444 μg/g of freeze-dried bloom materials.

Previous studies reported that exposure to HABs can increase potential risks of human health, such as non-alcoholic liver diseases and ALS (Caller et al., 2009; Lee et al., 2019; Pablo et al., 2009). Other reports demonstrated that BMAA was detected in ALS/Parkinsonism dementia complex patients in Guam (Bradley&Mash, 2009, Murch et al., 2004). These results can support the evidence that the cyanobacterial BMAA contributed to a risk factor of age-related neurodegenerations. In addition, Caller et al. (2009) identified that BMAA was linked to development of ALS and neurodegenerative diseases. However, there are very limited studies that have investigated potential linkages between HAB exposures and disease occurrences in Asia. Our previous study identified significantly positive association HABs intensity and non-alcoholic liver disease incidence rates in S. Korea (Lee et al., 2019). There was an urgent need for determining the risks for other types of diseases that can be related to HAB exposure in those bloom-affected areas. In this study, with statistical analysis that factored in both time period and distance, the associations between HAB intensity and human NDs, such as MND, AD, and PD, were identified. One notable finding in this study is that HABs have the most long-lasting effect on PD. Another highlight of this study is that distance of HAB can be a significant factor that impacts on the occurrence of ND. These results imply that HABs can pose long-term impacts on human health, especially people who reside close to the bloom-prone major rivers in S. Korea.

Potential routes of cyanotoxin exposure from HABs include ingestion of untreated water; consuming fish, shellfish and crops; and/or inhalation of aerosolized toxins. Our results also provide evidence that countries suffering from chronic HABs should make an effort to reduce HAB in their freshwater bodies as well as minimizing exposure to HABs. For future epidemiological studies, samples from personal air samplers, nasal swabs, urine or blood samples for measurements of cyanotoxins including BMAA can be helpful for understanding the extent of true cyanotoxin exposure and how the neurogenerative and other bloom-related diseases develop.

Although roles of toxic HAB in neuropathy are still controversial, statistical results of this study implies significant correlation between HAB incidence and occurrence of neurodegenerative diseases. Furthermore, our findings contribute to greater understanding of toxic HAB with potential health risks because environmental alteration resulting from human impacts has increased HAB proliferation and persistence. The modified statistic model with a grid-level population in this study can be applicable to other studies about determining correlations between potential health risks and other types of environmental contaminants.

It should be noted that the findings from this study do not manifest a causal relationship between the HAB severity and the human neurodegenerative diseases. However, this study provides statistical evidence that the HAB severity was a significant factor related to health risks, especially occurrence of neurodegenerative diseases that have not been reported before.

The major limitation of this study is that chl-a values were used as an indicator for HAB intensity, instead of cyanotoxins because toxin data from the study sites and during the duration covered in this study were

very much limited. Therefore, there is a possibility that using chl-a as a bloom indicator may over- or under-estimate potential health risk.

Abbreviations

AD: Alzheimer's disease

ALS: amyotrophic lateral sclerosis

BMAA: β-methylamino-L-alanine

GLM: generalized linear model

GLMM: generalized linear mixed model

HAB: Harmful algal bloom

MND: motor neuron disease

ND: neurodegenerative disease

PD: Parkinson's disease

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication: All the authors agreed on the manuscript.

Availability of data and materials

The data of neurodegenerative diseases, chlorophyll-a, and gridded population used in the study can be accessed at https://github.com/timonpig/Korea-HAB-Neurodegerative-Disease.

Competing interests

The authors declare no competing interests.

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Authors' contributions

SL: Investigation, Writing- Original Draft; **BC:** Methodology, Supervision, Writing- Review & Editing; **SJK:** Formal analysis, Visualization, Writing- Review & Editing; **JK:** Investigation, Data curation, Writing-Review & Editing; **DK**: Writing- Review & Editing; **JL:** Conceptualization, Methodology, Supervision, Writing- Original Draft.

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Figures

Figure 1

The locations of chlorophyll-*a* monitored sites (red dots) and 1-km grids (grey lines) for extracting population information in South Korea. Upper right window shows zoomed-in information on Seoul area (darker blue means higher population number) as an example.

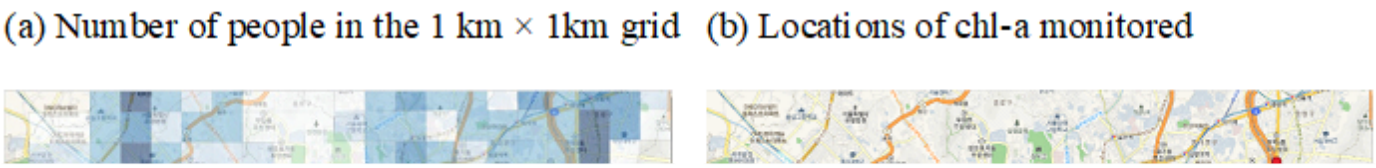

Figure 2

Approach used for digitization of chlorophyll-*a* monitored sites. Examples are shown using the sites located in Seoul that has a large river transecting the city and many tributary steams.

Figure 3

Heatmaps of average concentrations of chlorophyll-*a* (a), the average adjusted numbers of MND patients (b), AD patients (c), and PD patients (d) in a 1-km grid. Data are visualized here using the last three years of the study period (2015-2017).

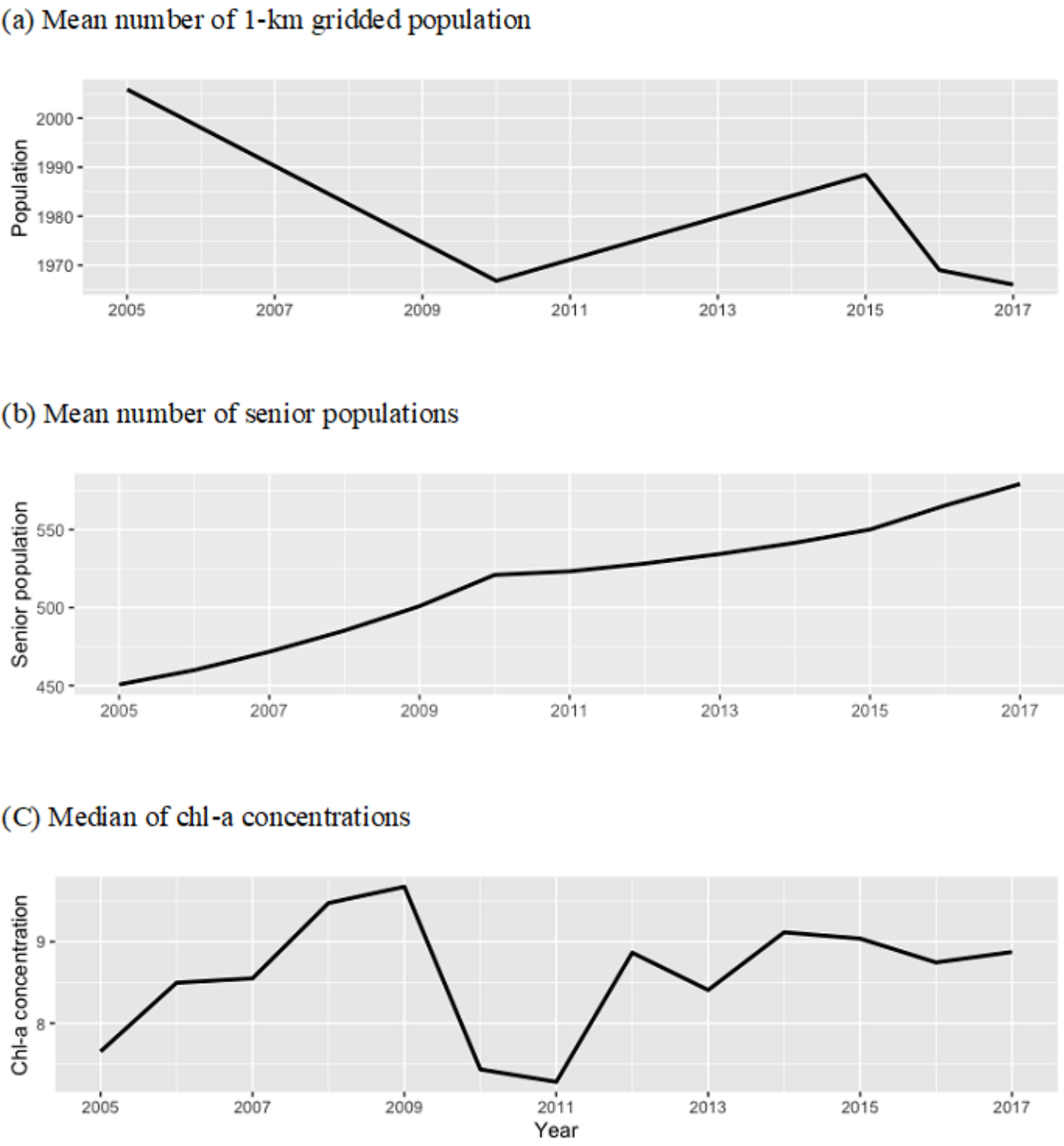

Figure 4

Trends of 1-km gridded population over time (a), numbers of senior population older than 65 (b), and observed average chlorophyll-*a* concentrations (c) from 2005 to 2017 in S. Korea.

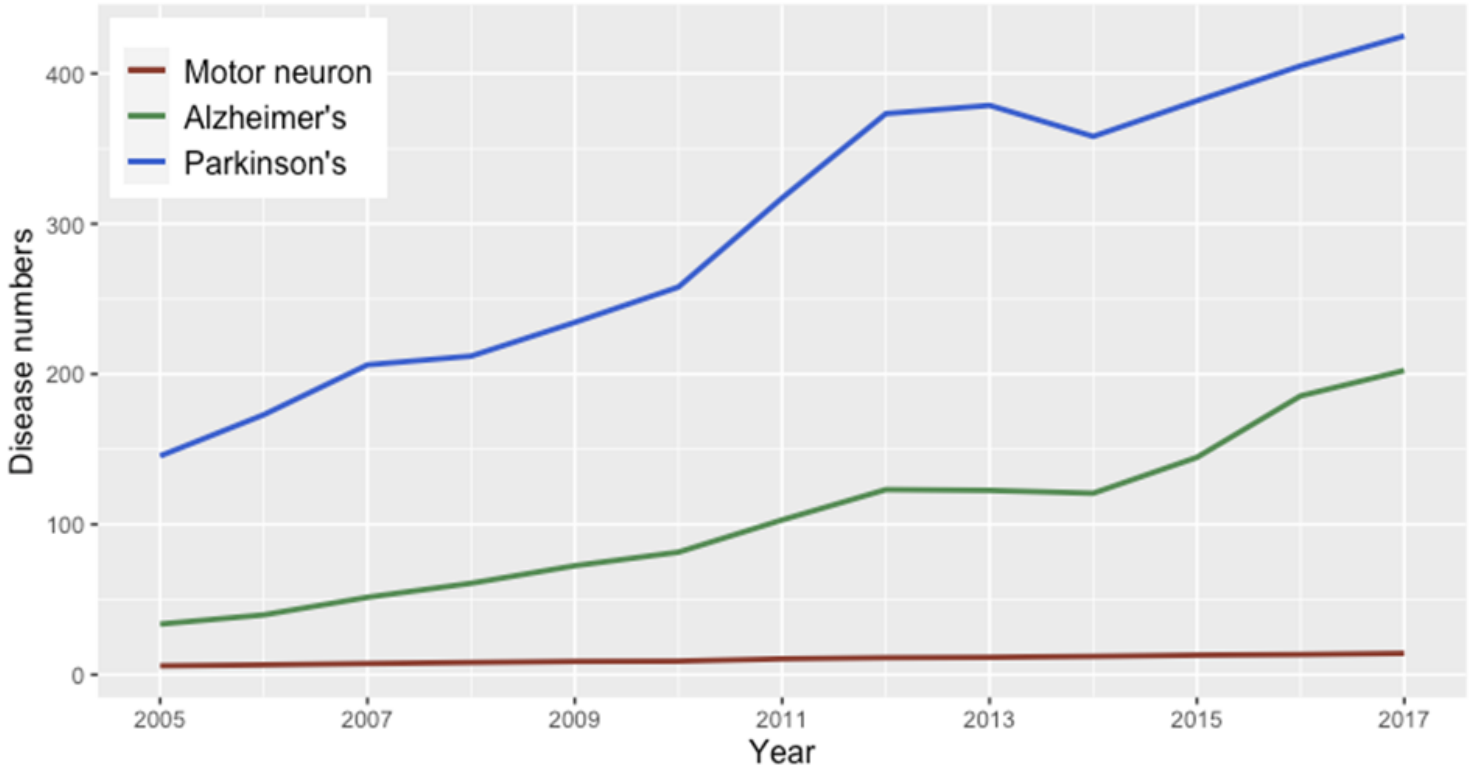

Figure 5

Comparison of the numbers of three types of neurodegenerative diseases in 1-km gridded population from 2005 to 2017 in S. Korea (Blue: Parkinson's disease; Green: Alzheimer's disease; and Brown: motor neuron disease).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- KoreaHABNDSupplementarymaterialsfinal7.18.20222.docx