

Disproportionate Residence of Multiple Sclerosis Patients in Southeast Wisconsin: A Clue to Environmental Factors?

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Introduction

- Environmental and lifestyle factors can contribute to the development of multiple sclerosis (MS) along with genetic predisposition
- Earlier studies reporting on geographic MS clusters support the hypothesis that location of residence can affect exposure to various organic and inorganic substances linked to the development of MS

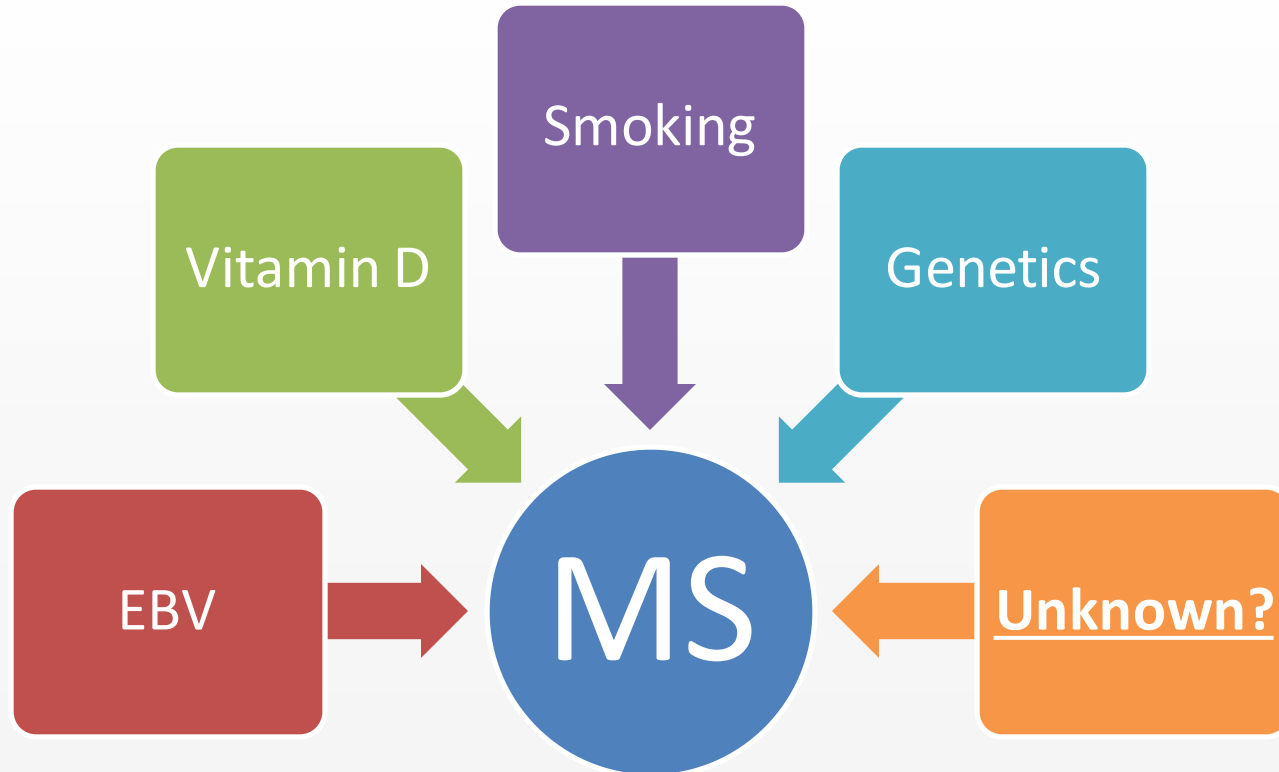


- Ascherio A, Munger KL, Lünemann JD. The initiation and prevention of multiple sclerosis. *Nature reviews Neurology*. 2012;8(11):602. doi:10.1038/NRNEUROL.2012.198



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Introduction



Introduction

- There is a global rise in MS, most notably in United States, Canada, Italy, Sardinia, Germany, Finland, and Sweden
- Gradient of increased MS cases in northern regions of United States
- Wisconsin is disproportionately affected by environmental factors such as decreased vitamin D due to low sun exposure
 - However, this cannot solely explain increased MS rates



- Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Multiple Sclerosis Journal*. 2020;26(14):1816-1821. doi:10.1177/1352458520970841
- Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology*. 2019;92(10):e1029. doi:10.1212/WNL.00000000000007035



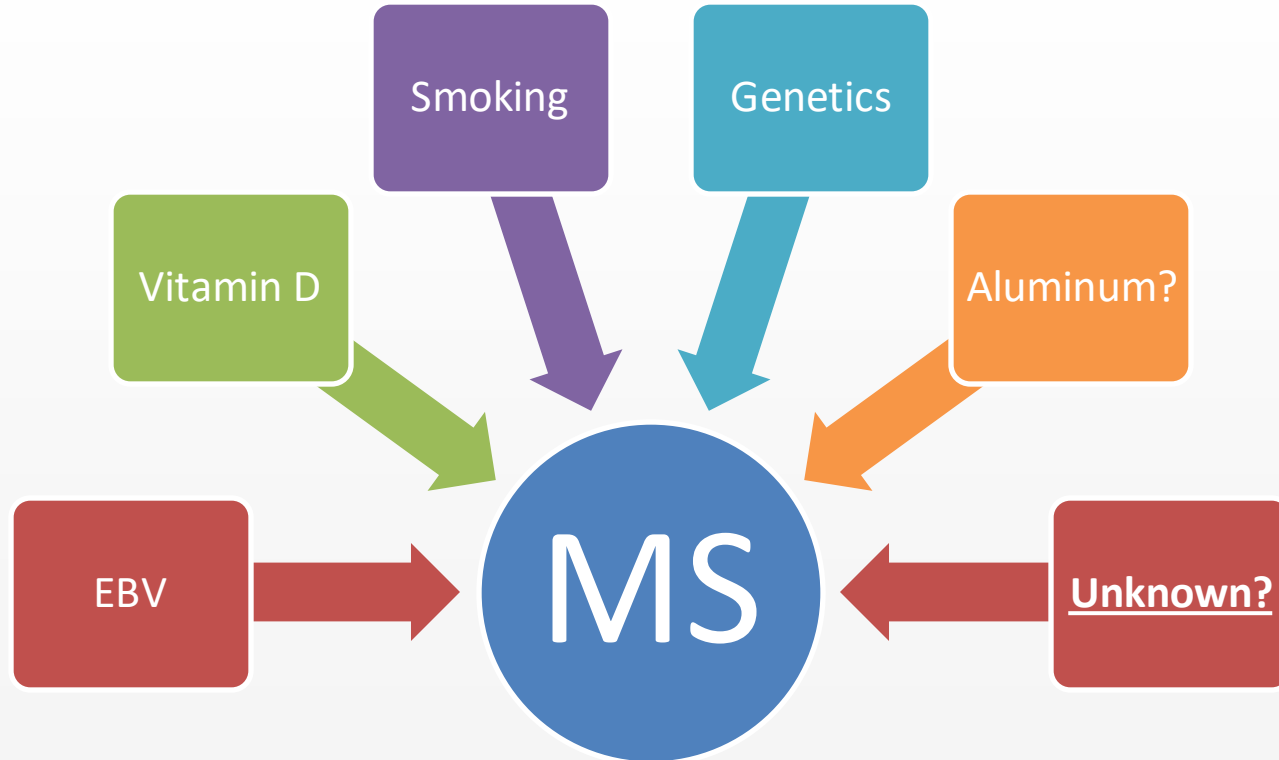
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Introduction

- In addition to macrogeographic disproportionalities, understanding of MS and conducting impactful interventions requires analysis of more precise geographical data
 - Ideally on a ZIP code level
- Anecdotally, disproportionalities in residence were noticed in our MS clinic in Milwaukee, Wisconsin, located in Southeast Wisconsin
 - Noticed many patients living near an aluminum factory



Introduction



Objective

To investigate for possible location clusters of MS patients in Southeast Wisconsin

Explore the potential for environmental exposures.

Create observations about the possibility of higher clusters of MS located near areas of potential aluminum exposure

Methods

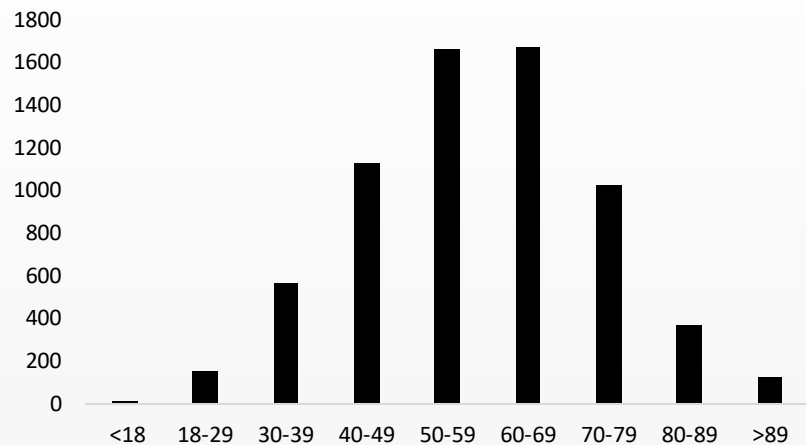
- Retrospective, epidemiological study of MS patients within the Froedtert and Medical College of Wisconsin health network, located in Southeast Wisconsin
- All MS diagnosed patient files within the Froedtert and Medical College of Wisconsin health network were retrieved using the i2b2 database and Honest Broker toolkit
- Patient ZIP codes were utilized to extrapolate state and city data using a global geographical database called GeoNames; data from ZIP codes outside of Wisconsin were excluded
- 2010 United States Census ZIP Code Tabulation Area data was used to compile population numbers by ZIP code in Wisconsin. Microsoft Excel 365 (version 2108) was used to generate heatmaps for total MS patients, MS patients per 100,000 population, and Wisconsin population by ZIP code

Results

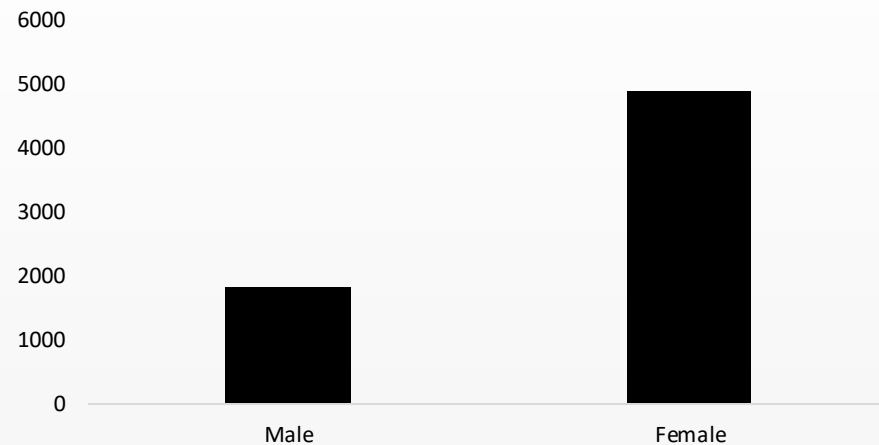
- Total of **6697 patients** were identified (73% Female)
- Clustered near the MS center (ZIP 53226)
 - Expected due to proximity to patients served
- Density of MS patients within 100 kilometers of the MS center was **240 per 100,000 population**
- Disproportionalities were noted in patient density when compared to total population data

Demographics

Age Distribution



Sex



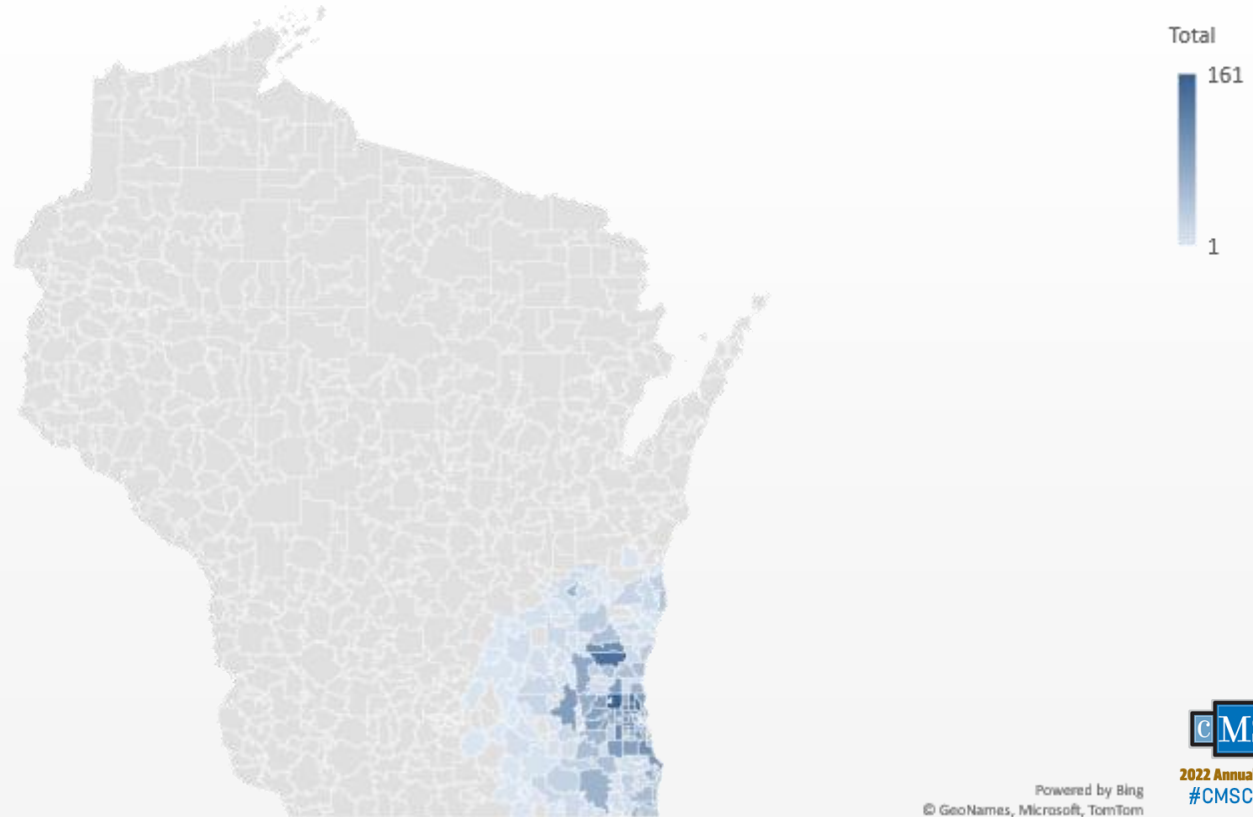
Twenty highest MS cases by ZIP codes within 100 kilometers of the MS center

County	City	Zip Code	Distance (KM)	Total MS	Population	MS per 100,000
Washington County	West Bend	53095	41	141	27587	511
Washington County	West Bend	53090	46	106	21415	495
Milwaukee County	Milwaukee	53226	0	93	18907	492
Washington County	Germantown	53022	20	91	19041	478
Milwaukee County	Milwaukee	53223	14	132	28596	462
Waukesha	Menomonee Falls	53051	13	161	36806	437
Milwaukee County	Milwaukee	53213	3	119	27573	432
Milwaukee County	Milwaukee	53222	4	110	26509	415
Milwaukee County	Milwaukee	53225	7	106	26840	395
Milwaukee County	Milwaukee	53214	4	132	35460	372
Waukesha	New Berlin	53151	9	111	31360	354
Waukesha	Muskego	53150	18	88	25622	343
Milwaukee County	Milwaukee	53209	11	152	46008	330
Milwaukee County	Milwaukee	53217	15	93	29184	319
Milwaukee County	Milwaukee	53216	7	100	34313	291
Milwaukee County	Milwaukee	53218	8	121	42780	283
Racine	Racine	53402	37	94	33283	282
Milwaukee County	Oak Creek	53154	22	101	35843	282
Milwaukee County	Milwaukee	53219	7	96	34418	279
Milwaukee County	Milwaukee	53221	13	96	40209	239

Location of MS center Location of aluminum factory

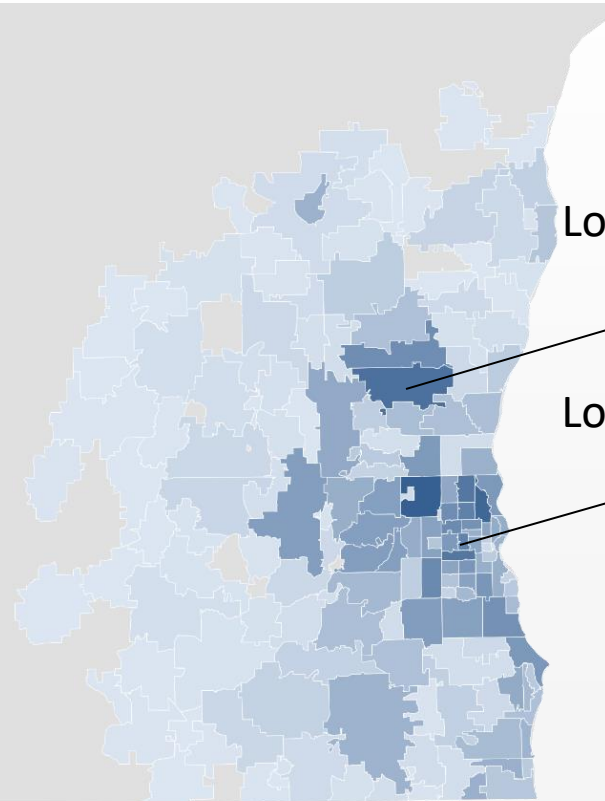


Density of MS (within 100km)



Density of MS (within 100km)

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Location of aluminum
Factory (53095)

Location of MS center
(53226)

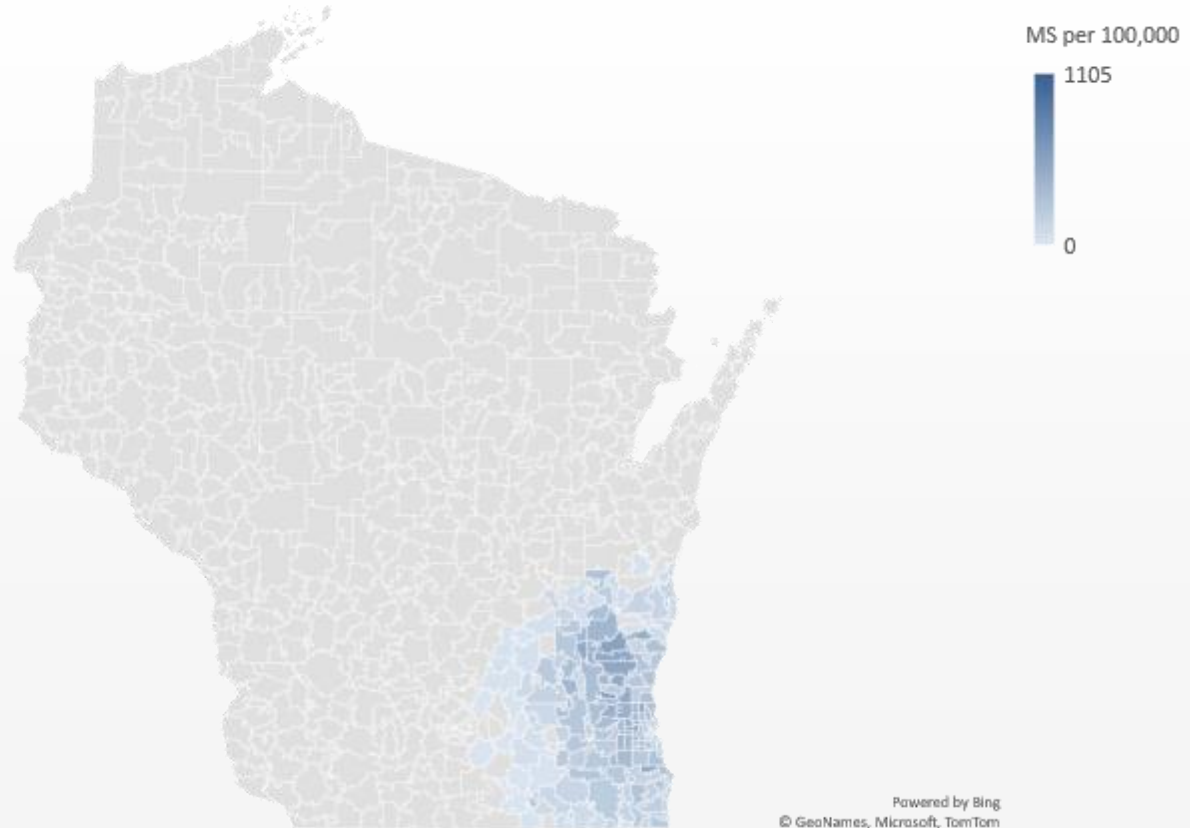
Twenty highest MS densities per 100,000 by ZIP codes within 100 kilometers of the MS center

County	City	Zip Code	Distance (KM)	Total MS	Population	MS per 100,000
Waukesha	Lannon	53046	15	13	1177	1105
Waukesha	Butler	53007	7	16	1835	872
Washington County	Hubertus	53033	26	33	4992	661
Waukesha	Elm Grove	53122	3	39	6172	632
Milwaukee County	Milwaukee	53295	39	1	181	552
Washington County	Kewaskum	53040	54	45	8154	552
Washington County	West Bend	53095	41	141	27587	511
Washington County	West Bend	53090	46	106	21415	495
Milwaukee County	Milwaukee	53226	0	93	18907	492
Washington County	Jackson	53037	32	49	9976	491
Dodge	Theresa	53091	60	9	1855	485
Washington County	Germantown	53022	20	91	19041	478
Waukesha	Okauchee Lake	53069	33	3	633	474
Milwaukee County	Milwaukee	53223	14	132	28596	462
Racine	Caledonia	53108	26	15	3270	459
Sheboygan	Random Lake	53075	58	15	3298	455
Waukesha	North Prairie	53153	32	11	2434	452
Waukesha	Sussex	53089	18	85	19151	444
Waukesha	Menomonee Falls	53051	13	161	36806	437
Milwaukee County	Milwaukee	53213	3	119	27573	432

Location of MS center Location of aluminum factory

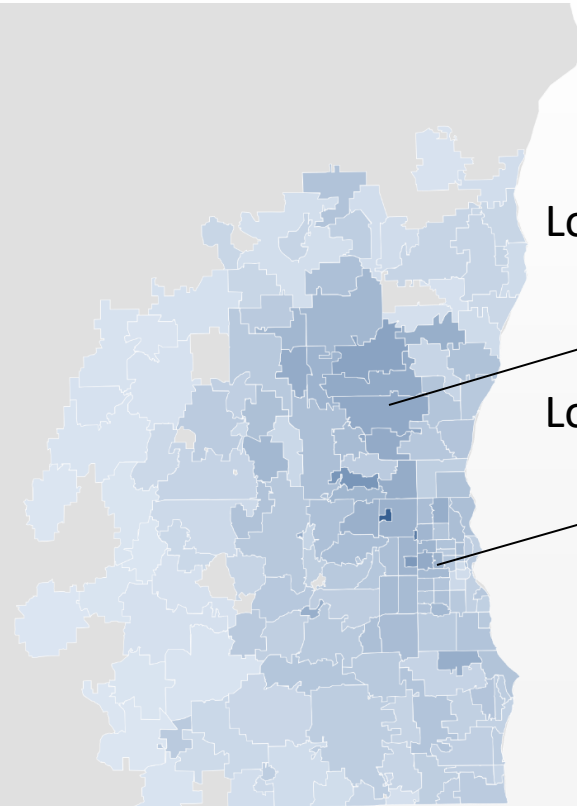


Density of MS per 100,000 population (within 100km)



Density of MS per 100,000 population (within 100km)

City	Zip Code	Distance (KM)	Total MS	MS per 100,000
Lannon	53046	15	13	1105
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Milwaukee	53226	0	93	492
Jackson	53037	32	49	491



Location of aluminum
Factory (53095)

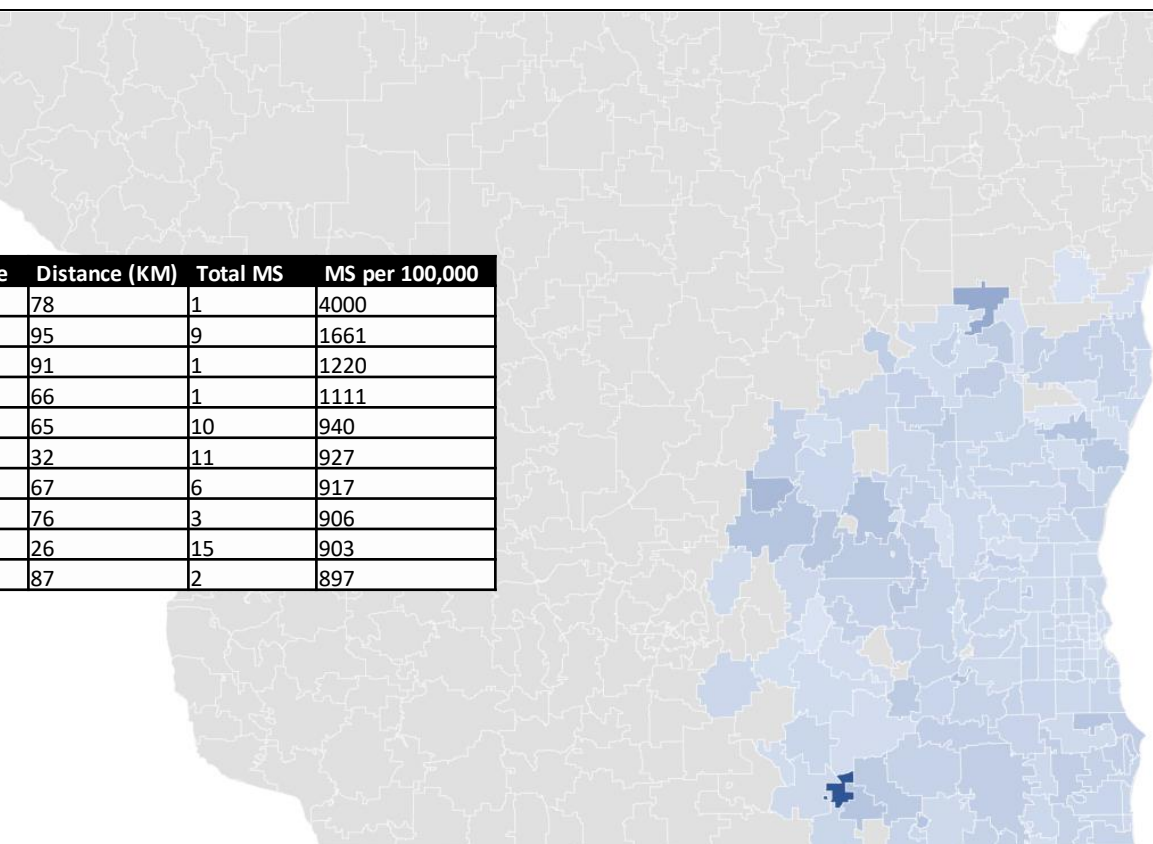
Location of MS center
(53226)

Twenty highest MS densities of total hospital patients by ZIP codes within 100 kilometers of the MS center

Placeholder slide for the above titled table (results pending)



Density of MS per 100,000 of total hospital patients (within 100km)

A map of Ontario, Canada, showing the density of Multiple Sclerosis (MS) per 100,000 total hospital patients within a 100km radius. The map is color-coded by region, with darker blue indicating higher density. The highest density is shown in the central and eastern parts of the province, particularly around the Greater Toronto Area and the Golden Horseshoe. Other regions with moderate density are shown in lighter blue, while the western and northern parts of the province are shown in light grey, indicating lower density.

City	Zip Code	Distance (KM)	Total MS	MS per 100,000
Avalon	53505	78	1	4000
Malone	53049	95	9	1661
Fall River	53932	91	1	1220
Hingham	53031	66	1	1111
Juneau	53039	65	10	940
North Prairie	53153	32	11	927
Williams Bay	53191	67	6	917
Darien	53114	76	3	906
Caledonia	53108	26	15	903
Columbus	53925	87	2	897

Discussion

- We report disproportional densities of MS patients cared for within a single large academic center in Southeast Wisconsin
- Patients were clustered near the hospital center, as expected
- However, we **noted several areas further away with higher densities that cannot be solely explained by proximity**

Discussion

- Wisconsin is disproportionately impacted by some environmental factors such as decreased vitamin D due to lower sun exposure
- More precise differences within Southeast Wisconsin cannot be solely explained by these environmental factors which affect the entire state

Discussion

- The examination of precise prevalence measurements within the United States is difficult due to the lack of unified healthcare records, recent estimates of MS are 363 cases per 100,000 population
- Our overall density in Southeast Wisconsin was **240 per 100,000**
- 76 ZIP codes out of 171 within 100 kilometers of the MS center showed a density higher than 240
 - This calls to investigation of local environmental factors



- Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology*. 2019;92(10):e1029. doi:10.1212/WNL.0000000000007035



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Discussion

- Several recent studies have discovered high levels of aluminum in brain tissues of people with MS and other neurological disease
- **We noted clusters of MS patients near the ZIP code 53095, a location where a major aluminum factory operated until 2001**



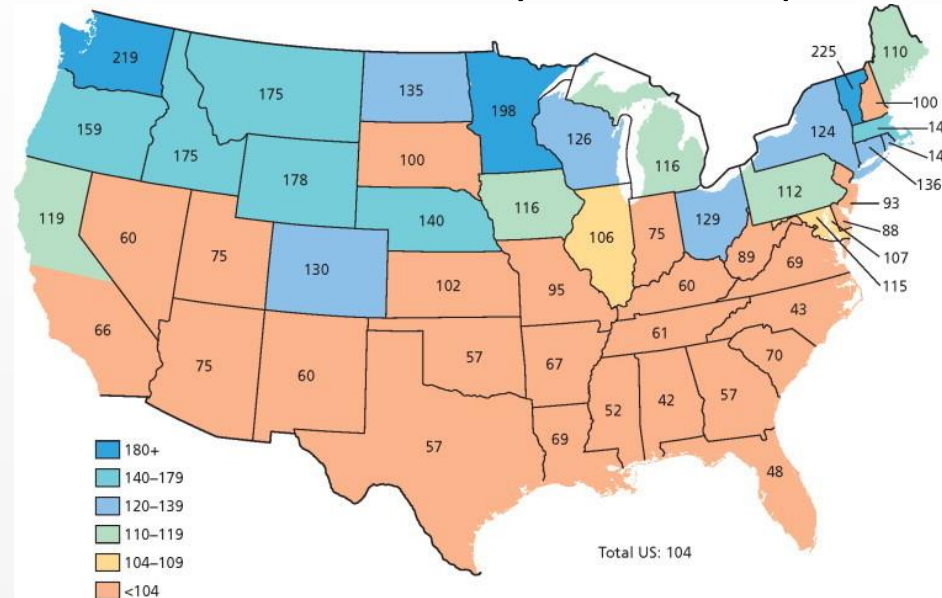
- Exley C, Clarkson E. Aluminium in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism. *Scientific Reports* 2020 10:1. 2020;10(1):1-7. doi:10.1038/s41598-020-64734-6
- Mold M, Chmielecka A, Rodriguez MRR, et al. Aluminium in Brain Tissue in Multiple Sclerosis. *International Journal of Environmental Research and Public Health*. 2018;15(8). doi:10.3390/IJERPH15081777
- Linhart C, Davidson D, Pathmanathan S, Kamaladas T, Exley C. Aluminium in Brain Tissue in Non-neurodegenerative/Non-neurodevelopmental Disease: A Comparison with Multiple Sclerosis. *Exposure and Health*. 2020;12(4):863-868. doi:10.1007/S12403-020-00346-9/FIGURES/2
- Lukiw WJ, Kruck TPA, Percy ME, et al. Aluminum in neurological disease – a 36 year multicenter study. *Journal of Alzheimer's disease & Parkinsonism*. 2019;8(6). doi:10.4172/2161-0460.1000457



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Discussion

- Outside of Wisconsin, there are multiple geographic areas with high prevalence of MS which also have nearby aluminum plants



Compston & Confavreux, 2006

Numbers based on Case-control ratios ($\times 100$) for multiple sclerosis by state of residence at entry into active duty for white male veterans of the Second World War.

Washington & Pacific Northwest

- Supplied 40 percent of the nation's aluminum in the 1980s
- Washington was also the site of a major aluminum plant, possibly a contributing factor to MS development

Sardinia

- Mediterranean island near Italy
- Prevalence estimates of MS are 299/100,000.
- The site of an aluminum plant until 2012, warranting further investigation in this population

Brescia & Lazio, Italy

- Disproportionate MS prevalence relative to other regions in Italy
- Study revealed metal contamination of garden soil with aluminum in Brescia
- Large aluminum recycling center is located in Lazio, Italy, which also happens to be a region with a high prevalence of MS



- Ferri R, Hashim D, Smith DR, et al. Metal contamination of home garden soils and cultivated vegetables in the province of Brescia, Italy: Implications for human exposure. *Science of The Total Environment*. 2015;518-519:507-517. doi:10.1016/J.SCITOTENV.2015.02.072
- Bargagli AM, Colais P, Agabiti N, et al. Prevalence of multiple sclerosis in the Lazio region, Italy: use of an algorithm based on health information systems. *Journal of Neurology*. 2016;263(4):751. doi:10.1007/S00415-016-8049-8



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Italy



Other Possible Associations

- Northern Ireland, prevalence of MS estimated around 200 per 100,000 → contains aluminum recycling factory
- Germany, prevalence of MS estimated around 150 per 100,000 → explosive rise in German aluminum production and processing in the 1950s
- **Several other observational links can be made regarding the presence of aluminum handling in regions with high prevalence of MS**

Possible Explanation?

- Aluminum is used as an adjuvant to boost the immune responses to vaccines
- Perhaps exposure to high levels of the metal can result in overactive and uncontrolled immune responses to other known risks (such as EBV)



• HogenEsch H, O'Hagan DT, Fox CB. Optimizing the utilization of aluminum adjuvants in vaccines: you might just get what you want. *npj Vaccines* 2018 3:1. 2018;3(1):1-11. doi:10.1038/s41541-018-0089-x



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Conclusions

- First study to examine prevalence and clusters of MS patients in Southeast Wisconsin
- Noted clusters of MS patients near the ZIP code 53095, a location where a major aluminum factory operated until 2001

Conclusions

- Recent literature shows possible associations between MS and aluminum, as well as epidemiological data
- Further investigations are essential to determine if exposures should be avoided or treated.
- **Although no conclusive links can be made, our findings call for further investigations for potential environmental exposures which could be contributing to the disproportionate distribution of MS cases in Southeast Wisconsin**

Future Directions

- Assess MS density of all patients within our hospital → further control for proximity and patient-base bias
- Investigate other locations with aluminum exposure and high cases of MS
- Measure aluminum burden in MS patients to assess for disease onset and severity

Acknowledgement

We'd like to thank the entire research team, the Medical College of Wisconsin, and the patients involved in this study for helping us progress MS research



Thank You For Listening!

Questions?

