THE OHIO STATE UNIVERSITY
COLLEGE OF PUBLIC HEALTH

Exposures Specialty Section Webinar

Monday May 3, 2021
12:00pm-1:00pm

SOT | Society of Toxicology
Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

BD2K analytics reveals the Zika virus epidemic as only one of multiple factors contributing to year-over-year 28-fold increase in microcephaly incidence

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Conflict of Interest Statement

The author declares no conflict of interest

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Outline of Presentation

Introduction: *Place! (zip code → census tract → census block)*

US EPA STAR Collaboration

Public Health Exposome framework and BD2K analytics

Exemplar: Brazil and Zika

- **Methodology**
- **Results**
- **Conclusions**
- **Discussion**

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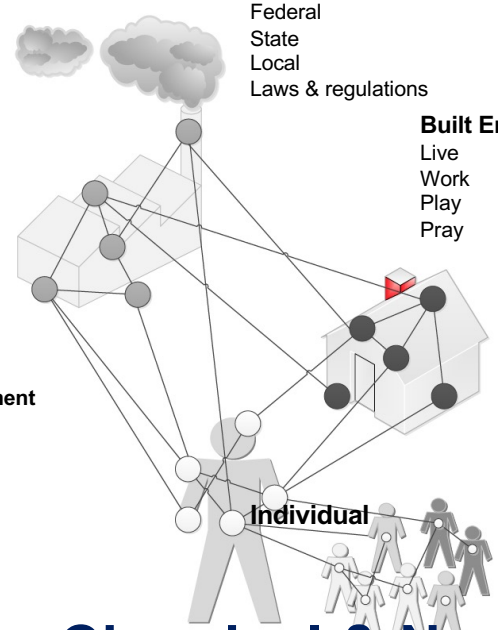
Place matters with regard to health care disparities and disparate health outcomes

Policy Environment
Federal
State
Local
Laws & regulations

Social Environment
- Race/Ethnicity
- Education
- Income/Employment
- Health Insurance
- Culture

Built Environment
Live
Work
Play
Pray



Physical Environment
- Air
- Water
- Soil

Individual

***Public Health Exposome* Framework w/ BD2K Analytics**

Moderating Factors
Nutrition, Literacy,
Positive parenting
Social networks
Safe neighborhoods
Personal behaviors

Population Level Disparities
- Cardiovascular
- Diabetes
- Cancer
- LBW, PTB, IM
- m-ZIKV$^{(+/-)}$

Exposure to Chemical & Non-Chemical Stressors

Behaviors
Smoking
Alcohol
Drugs
Diet/Nutrition
Consumer Products

Disparate Health Outcomes
Morbidity/Mortality
Immune System/ **Immuno-suppression**
Neuro-cognitive developmental delay
Longevity and other chronic diseases

Omics
Metabolomics
Transciptomics
Microbiomics
Epigenomics
Genomics

US EPA STAR Investigative Team

Paul

Darryl

Pat

Wansoo

M. Al-Hamdan

Michael

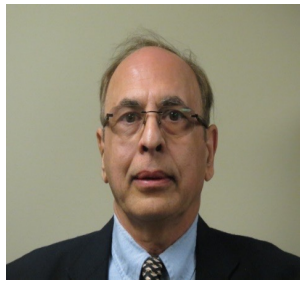
Maureen

Robert

US EPA STAR Investigative Team

Ramesh

Cynthia



M. Tabatabai

Reichard

Gary

Dave

C. Phillips

C. Mouton

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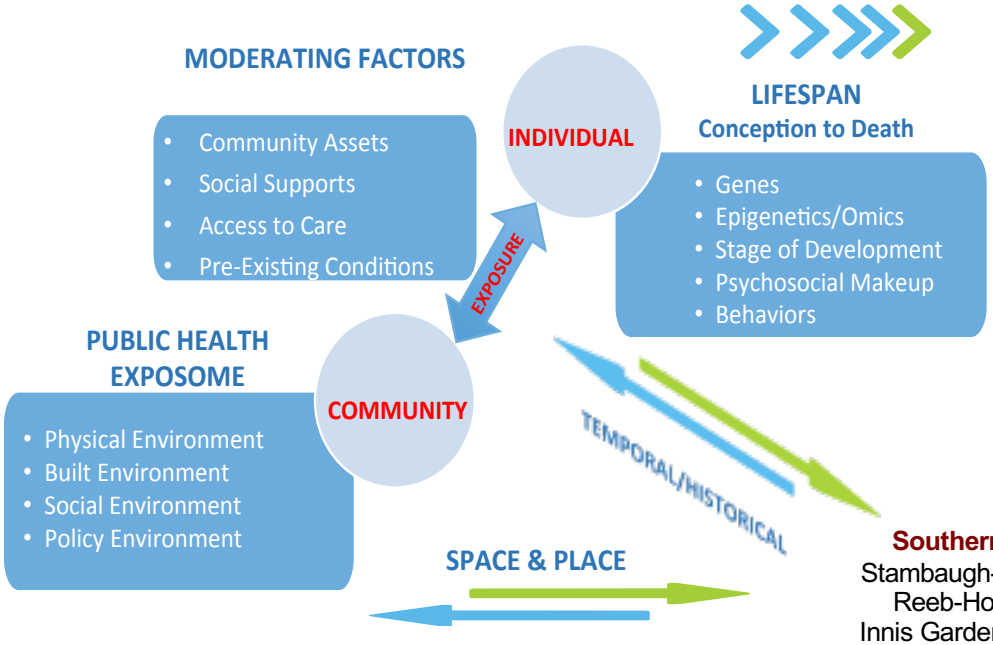
Public Health Exposome framework



Southern Gateway Communities
Stambaugh-Elwood Neighborhood (SE)*
Reeb-Hosack Neighborhood (RH)*
Innis Gardens Village Neighborhood (IG)
Merion Village Neighborhood (MV)
Vassor Village (VV)
Hungarian Village (HV)
Near East Neighborhoods (43203)

Supervised and unsupervised clustering, parametric and non-parametric, combinatorial algorithms and paraclique analysis

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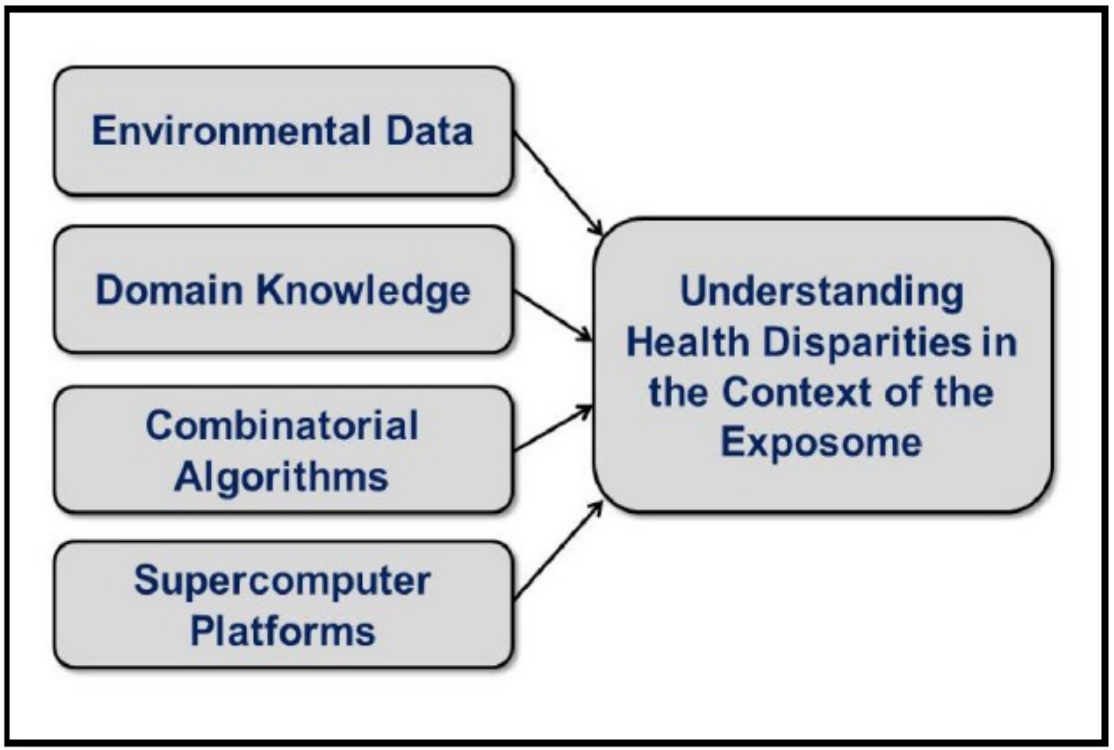
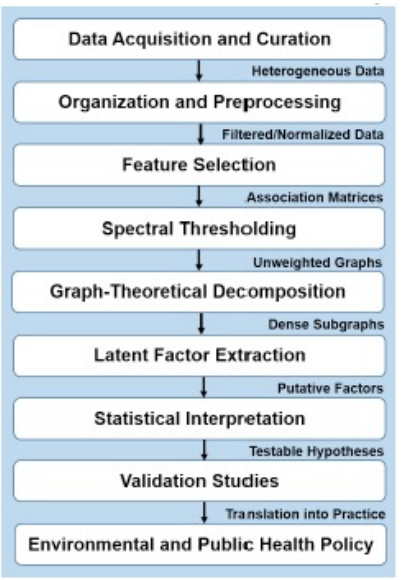
BD2K analytics to interrogate significance of "Place" in high-risk census tracts



PHE Tool Chain



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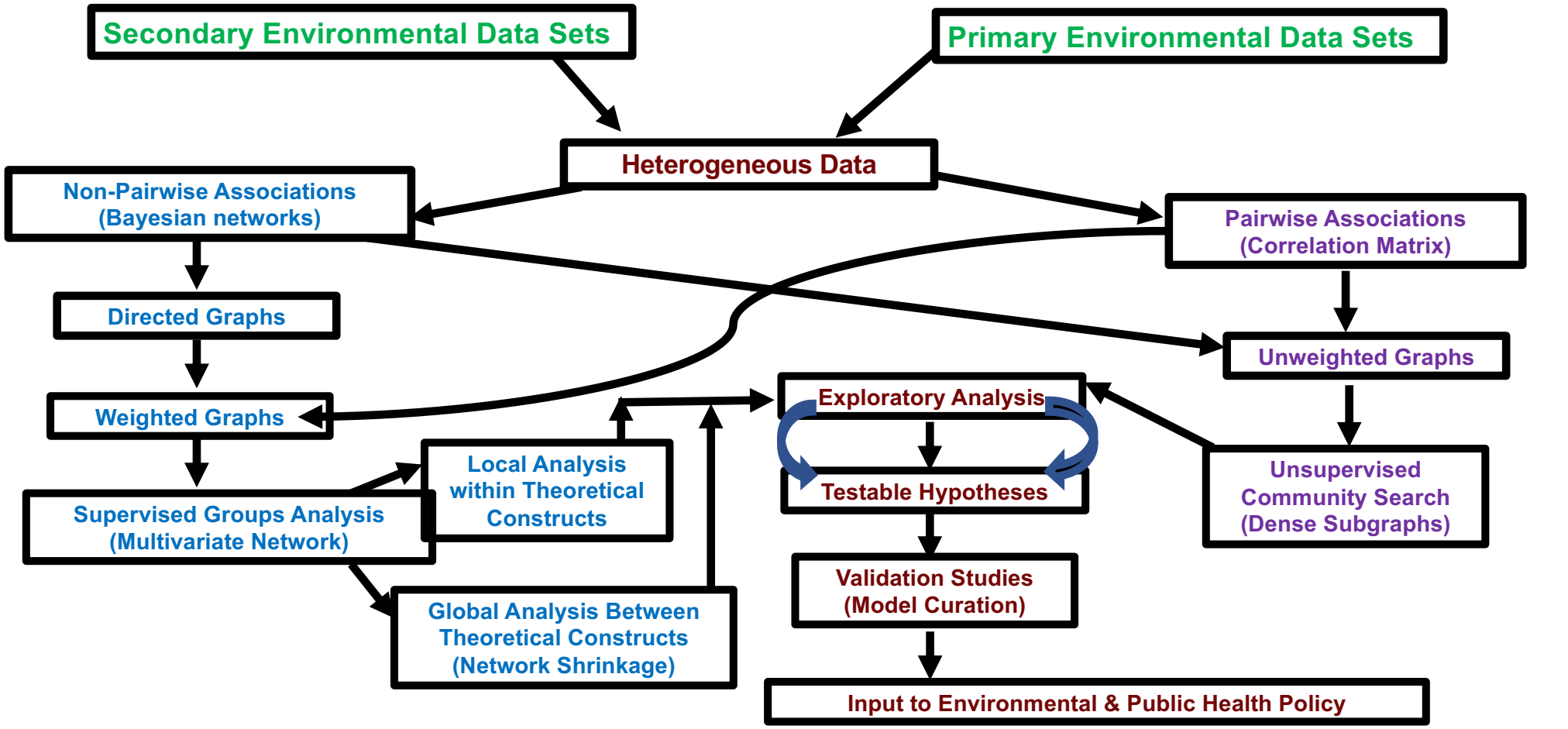
BD2K analytics to interrogate significance of "Place" in high-risk census tracts



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A network analysis of the incidence pattern of microcephaly in the context of Zika Virus Infection

Authors: Myriam Patricia Cifuentes[1,2*], Clara Mercedes Suarez[3], Ricardo Cifuentes[4], Nathan Doogan[2], Noel Malod-Dognin[5], Sam Windels[5], Jose Fernando Valderrama[6], Darryl B. Hood[2], Natasa Przulj[5]

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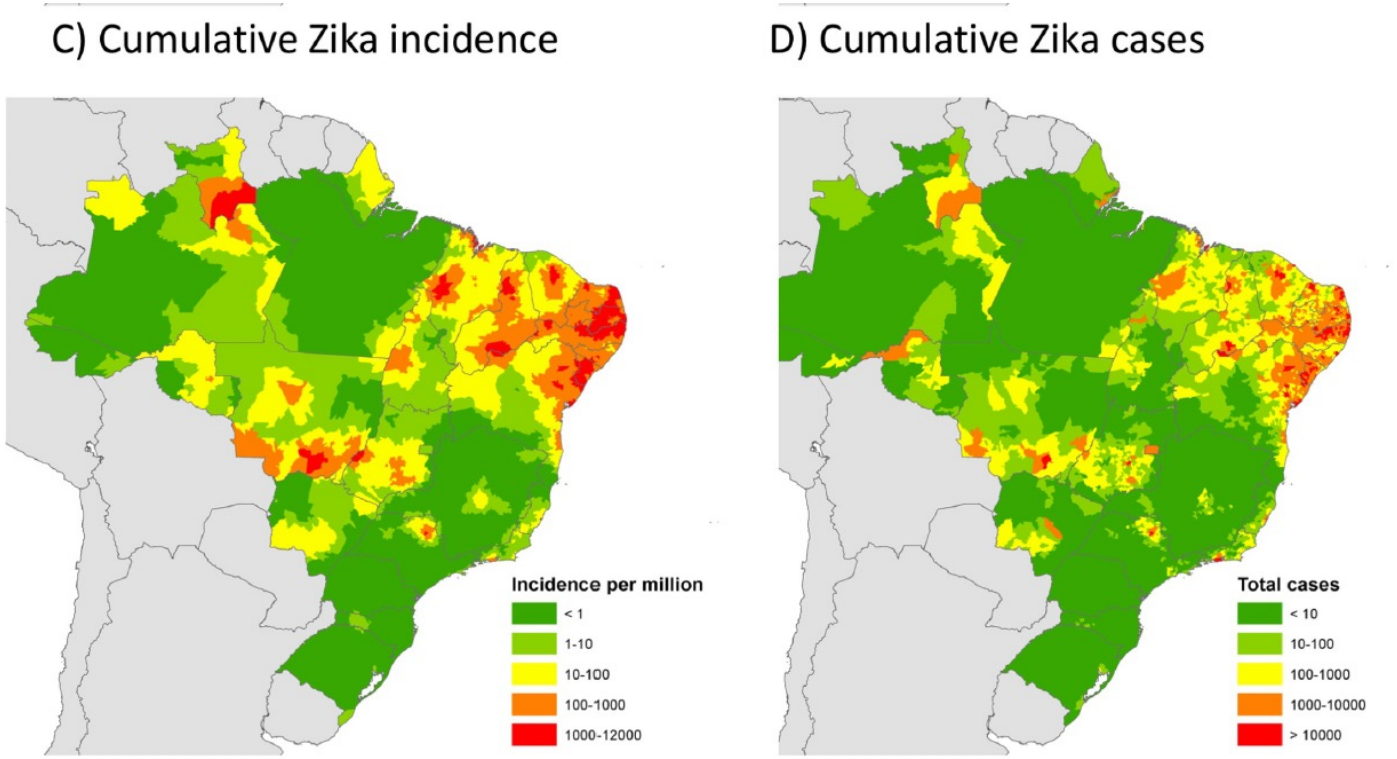
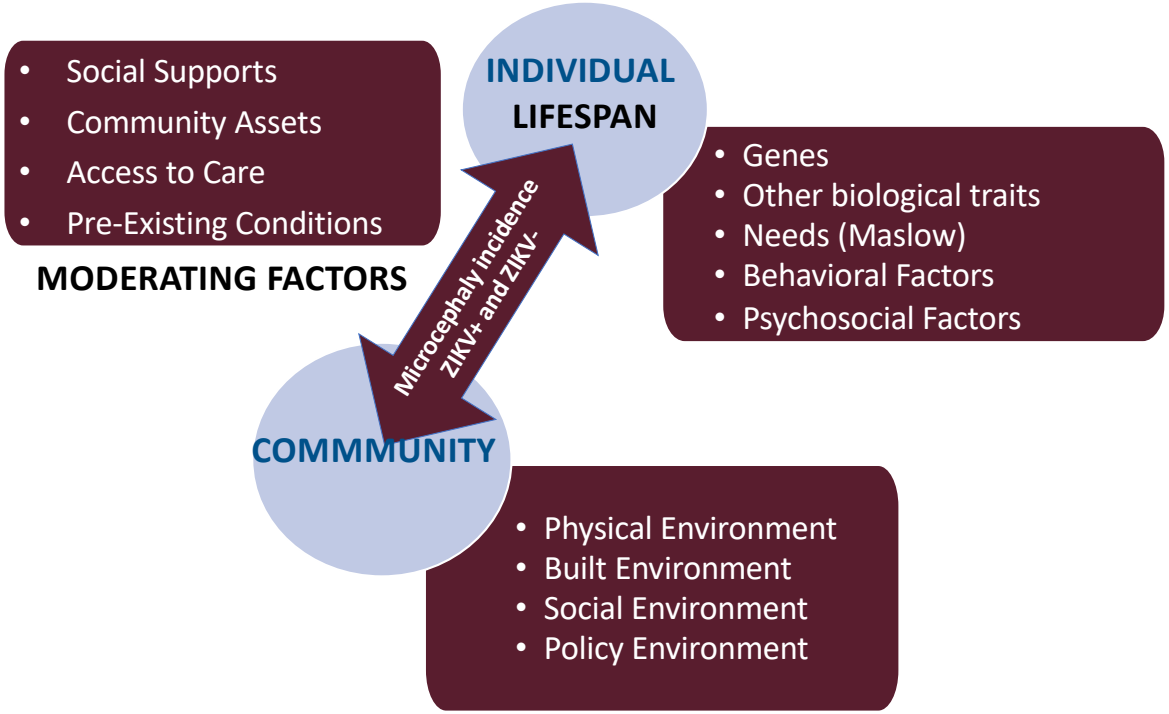


Figure 1. Geographic distribution of ZIKV infection did not match with microcephaly outbreaks during the 2015-2016 ZIKV epidemic

From; Brady OJ, Osgood-Zimmerman A, Kassebaum NJ, Ray SE, de Arau´jo VEM, da No´brega AA, *et al*. (2019) The association between Zika virus infection and microcephaly in Brazil 2015–2017: An observational analysis of over 4million births. PLoS Med 16(3): e1002755.https://doi.org/10.1371/journal.pmed.1002755

…alternative hypotheses as to other determinant factors that explain how the built, natural, physical and social environment interact with…



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Test the hypothesis that multiple factors are associated with microcephaly incidence positive for Zika infection (m-ZIKV^{+}).

1,810 cases of m-ZIKV^{+} and during 2016
3,924 cases of m-ZIKV^{-} during 2016
5,734 microcephalic babies in one year
117,326 low birth weight (LBW) cases
863,153 births (B)

Characterize specific patterns of associations with multiple factors, and contrast that pattern with the patterns of associations with those factors that were exhibited in three types of Controls:

1) **microcephaly incidence negative for Zika infection (m-ZIKV^{-}),**
2) **Low Birth Weight (LBW, indicator of infant morbidity), and**
3) **Births (B, as a proxy for healthy newborns)**

METHODOLOGY

Collected and curated public frequency data to calculate all controlled statistical associations among 382-variables describing 16-determinant factors, incidence of concurrent health outcomes, and m-ZIKV+ surveillance from 5,565 municipalities in Brazil.

Comparative Network Inferential Analysis

Scale	Determinant	Summary of variables in each determinant
Context determinants	1. Governance	Governance is depicted as the formalized convergence of diverse social factors of decision making, such as municipal planning agencies, mechanisms for empowering citizens and involvement in high-level policy agendas (*12*).
	2. Macroeconomic policy	Variables describe the balance through economic impositions and fostering and the resulting economic inequalities in population by **Gini and Theil indices** (*2, 12–14*).
	3. Social policy	Variables relating to social support in municipalities through proxies of ZEIS (Zonas Especiais de Interesse Social) for low income housing and inter-institutional social support and development (*2, 12–14*).
	4. Public policy	Variables describe diverse instruments such as plans and legislation that stabilize general public policies on environment, land use, urban settlement, development and housing, economy and transportation.
	5. Culture and social values	Variables relating to institutional concerns of cultural and educational affairs in municipalities (*12*).
	6. Demographic Epidemiologic conditions	Population age pyramid according to the 2010 census and 2015 population estimate for municipalities. Institutional concerns of health and sanitation in municipalities (*12, 15*).
Structural determinants	7. Income	Population percent and income distribution between rich, vulnerable, poor and poorest populations, and for workers and unemployed. We also included the mean income by race, and the GDP, per capita GDP and the human development index (HDI) and its income dimension in municipalities (*14, 16*).
	8. Education	Attainment and enrollment in basic school (primary and middle), literacy by race, sex and according to age thresholds, and the expected years of study. We included the dimension of 'education' of HDI (*14*).
	9. Occupation	Participation in the work force and unemployment, differentiated by race, educational attainment and work sector, and commuting (*12, 14, 16*).
	10. Social Class	Social class by individuals and households located in agglomerates qualified as subnormal, and variables labeling social vulnerability (*13*).
	11. Race-Ethnicity	Distribution by Brazil's racial groups (*2, 12, 13*).
Intermediary determinants	12. Social Networks/Socio-env. Psych. Circumstances	Civil status, people and children in households supported by people without education of who are vulnerable, and dependency ratio (*12, 14, 16*).
	13. Biological Factors	Population distributed by sex, and women population in fertile age groups, fertility rate, infant female and male populations, life expectancy, longevity and ageing rate. Longevity dimension of the Human Development Index (*16*).
	14. Childhood Development	Negative approach by Low Birth Weight (LBW) and less than 1 year undernourished children (*12, 16*).
	15. Material Circumstances	Dwelling material, availability and access to aqueduct/in-house pipe water, sewage system, and waste disposal. Access to electricity. Vegetation distribution and land use. Potential exposure to agro-toxic by agricultural use or residue disposal. Rapid assessment of indices for *Aedes aegypti* (*Levantamiento Rápido de Indices para Aedes aegypti* LIRAa) (*13, 17*). Low income Rate Assistance
	16. Health System (0.974)	Variables of investment (national and local) and performance of Brazil Health System in municipalities, prenatal care and normal delivery, primary and higher levels of care coverage and public health actions. We included as one of the main public health actions a very detailed documentation of vaccinations, number of doses (as a proxy of the strength of this intervention) and coverage (width of intervention over beneficiary population) for 2015 and 2016 (*15, 16*).
Health outcomes	17. Vector Borne Diseases	Severe dengue, Malaria and Chagas disease cases (*15, 16*).
	18. Other Health Results	Infant and childhood mortality, and incidence rate of congenital syphilis. Different poisoning incidence according to municipality of exposure, notification and residence (*18*). Place of exposure indicative of contact with toxic substances, while place of residence and notification correspond to the administrative process.
	19. Microcephaly Surveillance	Surveillance of microcephaly incidence, including incoming and investigated microcephaly cases, and confirmed/discarded ZVI cases during the first trimester of 2016 (*19*).
	20. Stillbirths Surveillance	Surveillance of stillbirth incidence, including incoming and investigated stillbirth cases, and confirmed/discarded ZVI cases (*19*).

Table 1. Determinants of health and health outcomes related to microcephaly attributed to ZVI included in the model. For each determinant are included Cronbach alpha values. [0.70 and above is **good**, 0.80 and above is **better**, and 0.90 and above is **best**].

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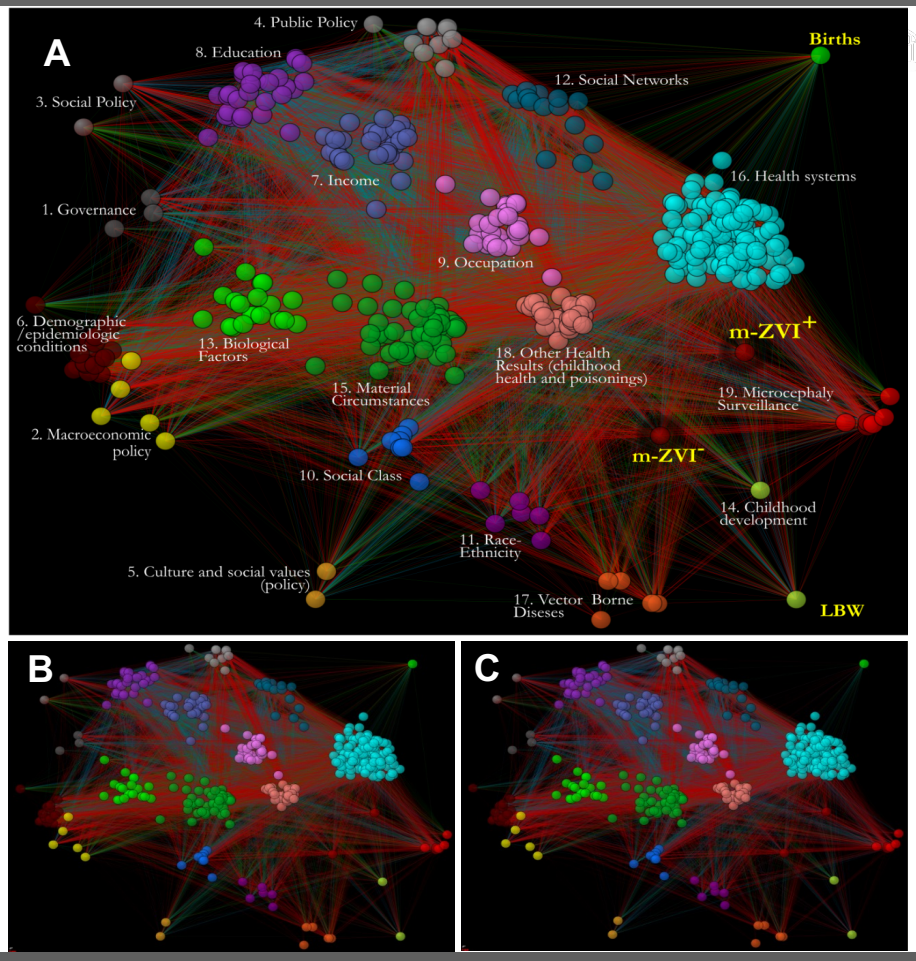
Methodology (Continued)

- To control associations from spuriousness and confounding, **squared higher order partial correlations ($pcor^2$) were used** as proxies for effect size, **complemented by zero-order correlations (zcor)** and **partial correlations (pcor),** each with the corresponding significant p-values evaluated after correction for multiple comparisons.

- **Macroanalyses** compared subnetwork structures by statistical tests between distributions of their network indices and by advanced network structural methods of graphlet distance.

- **Microanalyses** assessed the details explaining the differences by **comparing the fingerprints of all aligned subnetworks**.

- **Subnetwork fingerprints corresponded to visualizations of ordered weighted associations** between matching pairs of variables in each subnetwork.



Exposome Wide Association Study-based determination of ZVD context networks

Context networks derived from *Exposome* framework and BD2K analytics demonstrating associations of multiple determinant factors with Zika Virus Disease incidence in Brazil's municipalities during the 2015-2016 outbreak. Groups of variables within each determinant factor are shown.

Four colors show **strongest positive partial correlations (dark blue), strong (green), negative strongest (dark red),** and **strong (light red)** partial correlations among variables/nodes. A, shows the full network, including labels. B, corresponds to the threshold network by graphlet optimally far from random network. C, corresponds to threshold network clustering coefficient-based optimally far from random network. (**Cifuentes et al., 2021**)

RESULTS

Evaluated the patterns of factors associated with case and control phenomena by extracting the corresponding subnetworks. The case subnetwork included all interdependent nodes directly linked to m-ZIKV^{+} incidence **(Figure 2. Panel A).** Control subnetworks included all nodes directly linked with m-ZIKV^{-} incidence **(Figure 2. Panel B),** LBW **(Figure 2. Panel C),** and Births (B) **(Figure 2. Panel D).**

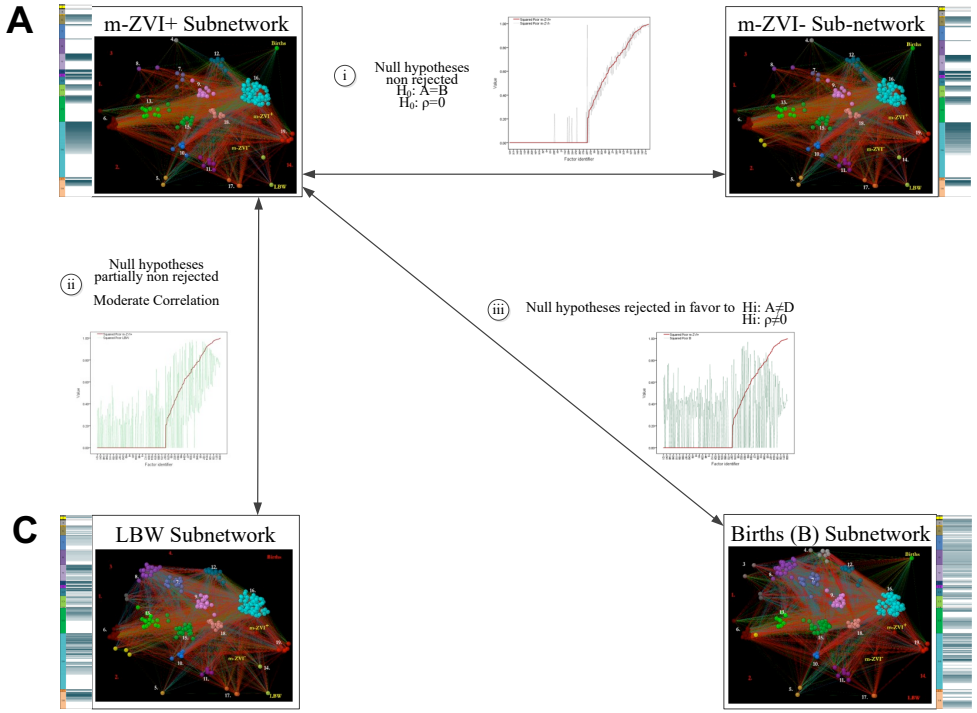


Figure 2. General pattern of factors associated with microcephaly is unspecific for m-ZIKV^{+}

Extracted Subnetworks (A-D) from the 0.65 threshold context network (Fig. 1) by the method of k=1-neighbors.

RESULTS

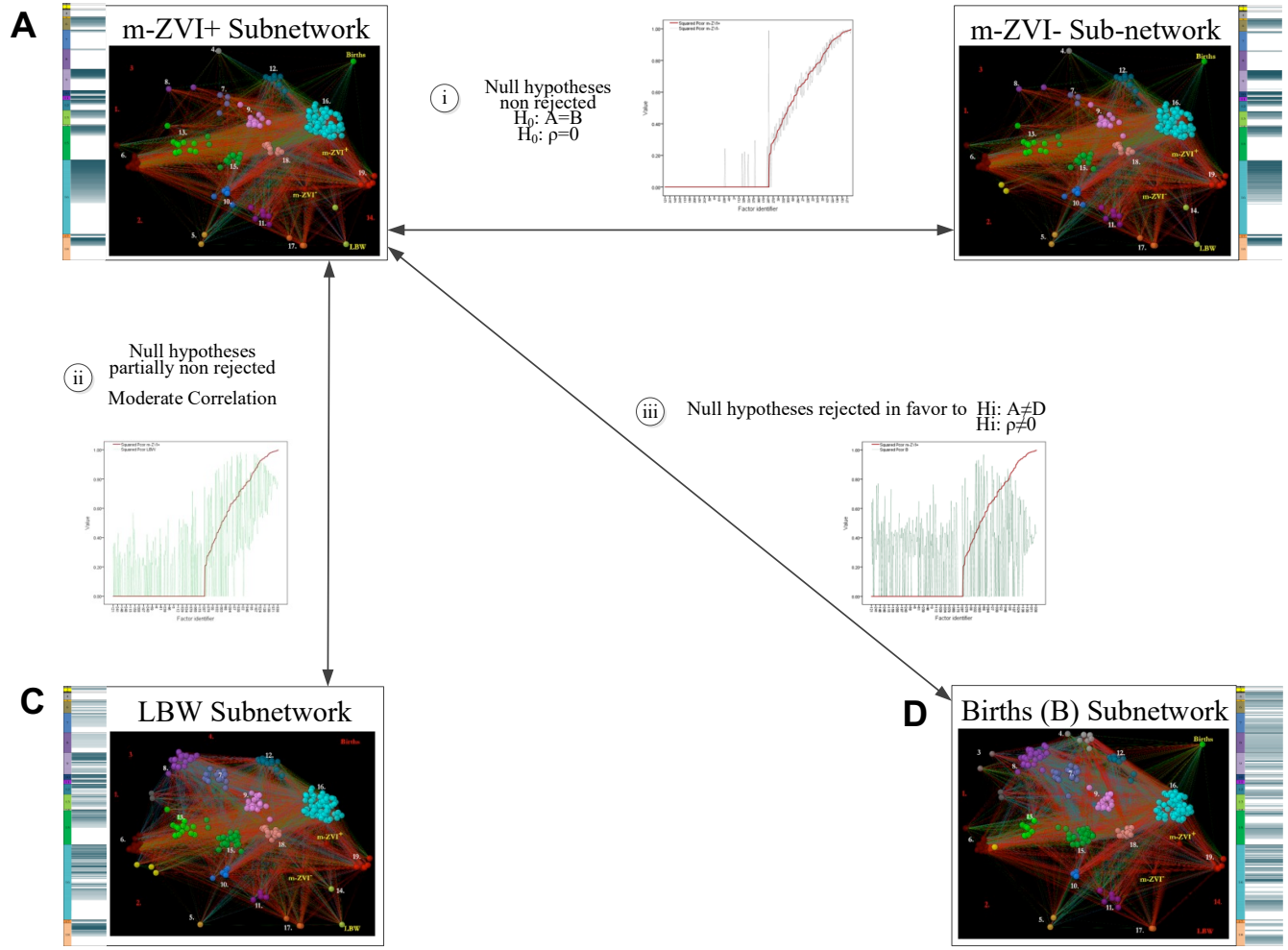


Figure 2. General pattern of factors associated with microcephaly is unspecific for m-ZIKV+

- Oscillation amplitude of control subnetworks $pcor^2$ show the smallest differences between m-ZIKV+ and m-ZIKV-
- Moderate differences between m-ZIKV+ and LBW (indicator of infant morbidity)
- Robust differences between m-ZIKV+ and B (as a proxy for healthy newborns)
- Flat red line indicates no connections.

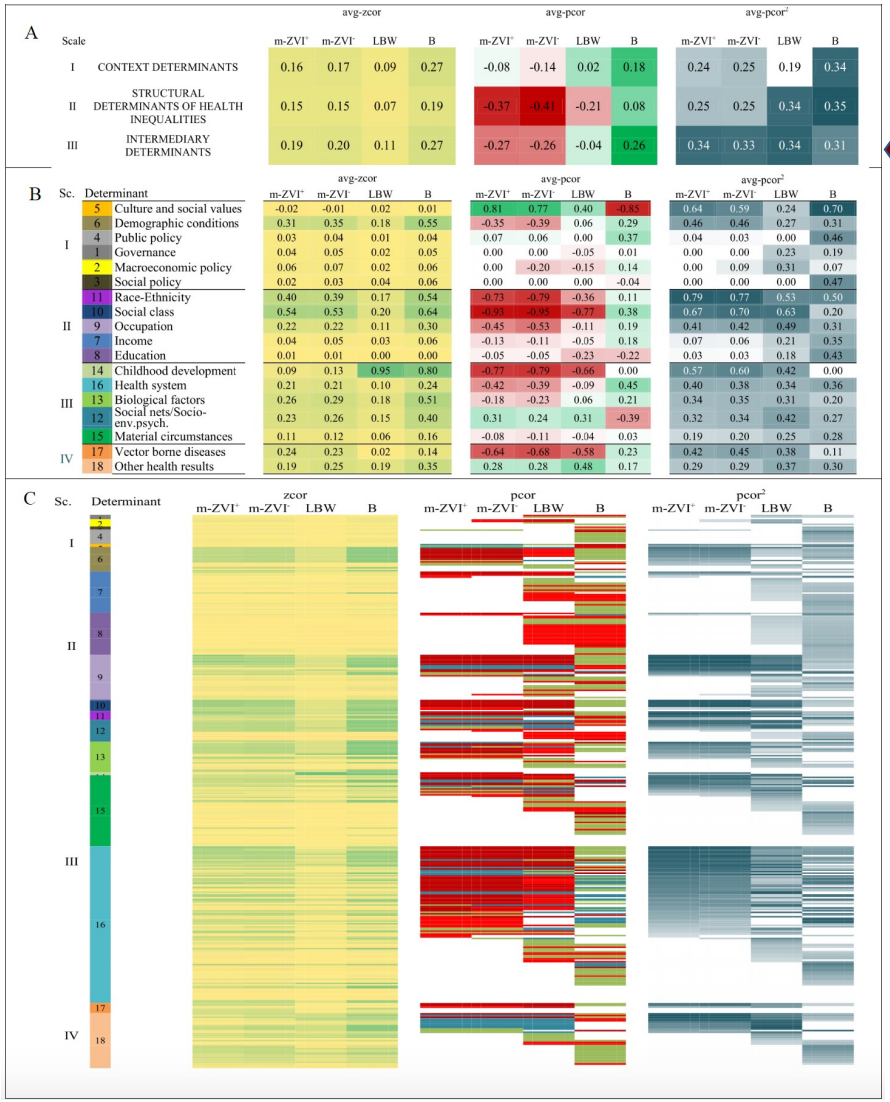


Figure 3. Factors that explained the non-specific pattern of associations of microcephaly incidence positive for Zika infection (m-ZIKV^{+})

- In general agreement with the recent work reported by Brady et al., 2019, comparisons by this method suggested that the patterns of factors associated with case m-ZIKV^{+} and control m-ZIKV^{-} subnetworks were analogous.
- Among the three, intermediary factors had a slightly higher influence.
- By contrast, for the LBW-subnetwork, factors in the social structure and intermediary scales were significant.
- For the B-subnetwork, factors in all three scales had low-to-moderate effects.

Legend: Heat bands summarizing patterns of association of each subnetwork. Values of zcor, pcor, pcor^2 are visualized by color gradients that are analogous to single columns of heat maps. The descending ordered pcor^2 within determinants of ZIKV^{+} is the reference pattern (first column, teal shade).
Panel A, bands by the three broad scales of determinants.
Panel B, Bands by Determinant factors.
Panel C, Bands by single variables within factors.

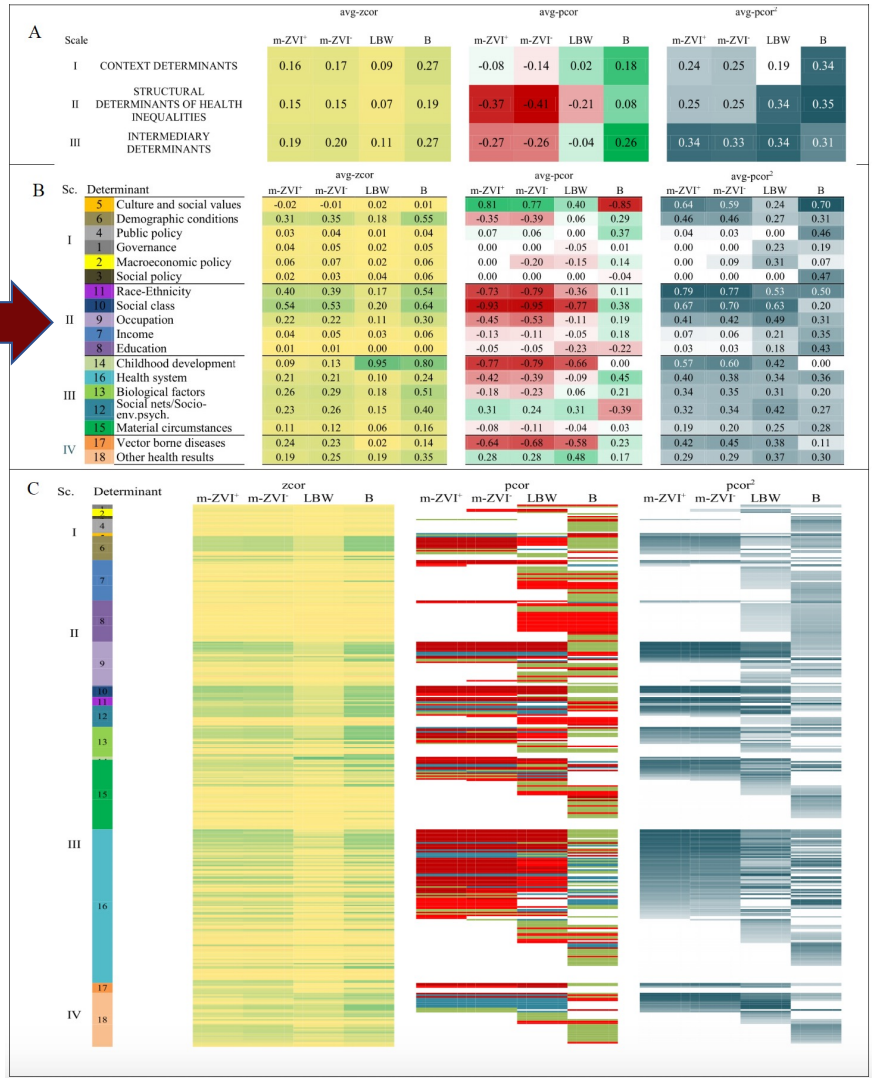


Figure 4. Factors in the scale of structural determinants.

- In the **microcephaly incidence positive for Zika infection** (m-ZIKV⁺) subnetwork, links with race/ethnicity and social class had the highest avg-pcor².
- The factor of social class mainly included variables describing vulnerability.
- Occupation' factor showed a moderate avg-pcor² by nodes of 'labor force,' "unemployment proportion' (general and by race), and 'unemployment in the environmental field' as the only specific occupational sector involved.
- Conversely, 'income' and 'education' factors had very low avg-pcor². Inside the income factor, 'mean income' and 'Theil index for work revenues' had high pcor², while 'income of 20% richest' and 'per-capita GDP' had moderate pcor²
- Inside the education factor, only 'enrollment of 5-6year-old' and 'illiteracy' were associated respectively, by moderate and low pcor². Minor differences of the m-ZIKV⁻-subnetwork were due to links with 'unemployment in the construction sector' inside the occupation factor, and linked absence with 'per-capita GDP' in the income factor **(Fig. 4B).**

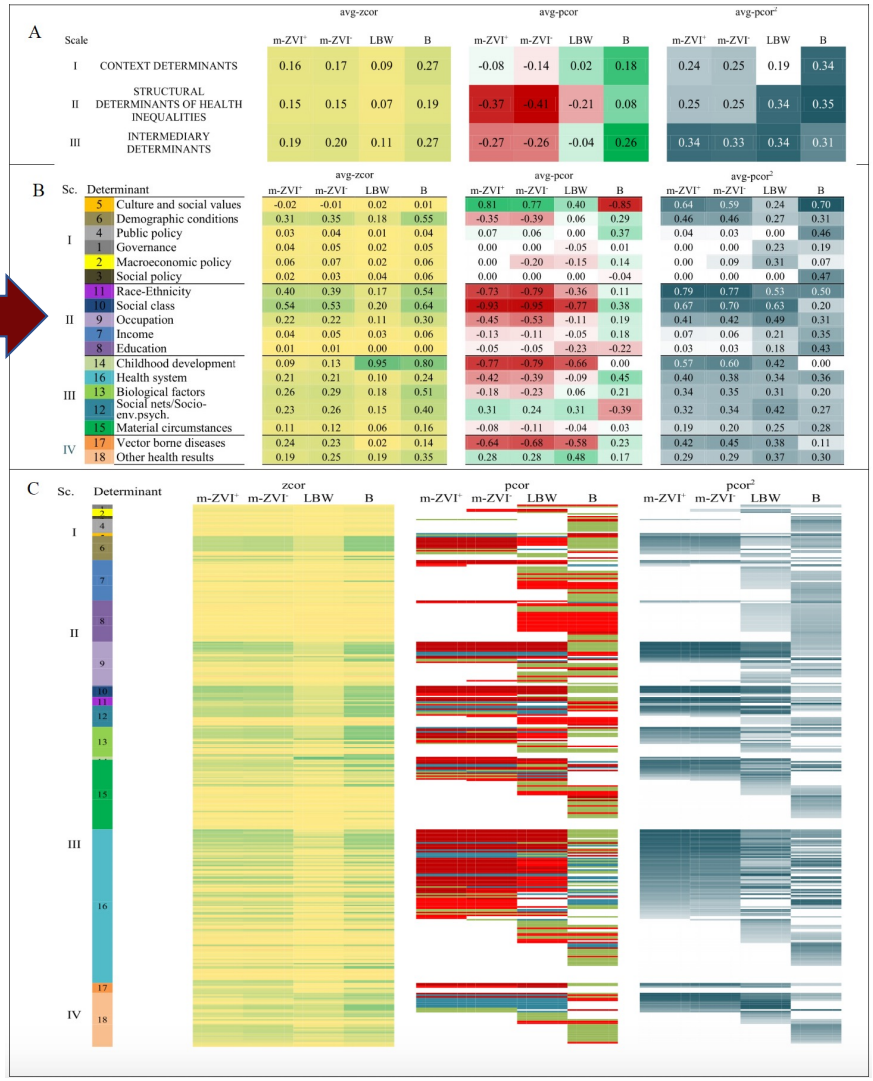


Figure 5. Factors in the scale of structural determinants.

In the control LBW-subnetwork, the determinants of race, social vulnerability, and occupation in the structural scale stood out based on avg-pcor^2.

Within the race determinant White, mixed, and Black had the highest pcor^2; all social vulnerability variables were linked except 'woman head of family'. These association patterns inside each of the determinants were similar to those in the **microcephaly incidence positive for Zika infection** (m-ZIKV$^+$) subnetwork.

In the control B-subnetwork, the determinant of race also had the highest avg-pcor^2, but, in contrast to the associations in the m-ZIKV$^+$-subnetwork, education, income, and occupation were relevant. Per capita GDP, illiteracy (determined without reference to race), primary school enrollment, participation in the labor force by members of yellow and indigenous races, and self-employment were remarkable nodes with high pcor^2.

While the LBW-subnetwork and the B-subnetwork have significant associations with a number of the same structural determinants, the most obvious observation is the fact that those associations have opposite signs for each subnetwork, respectively.

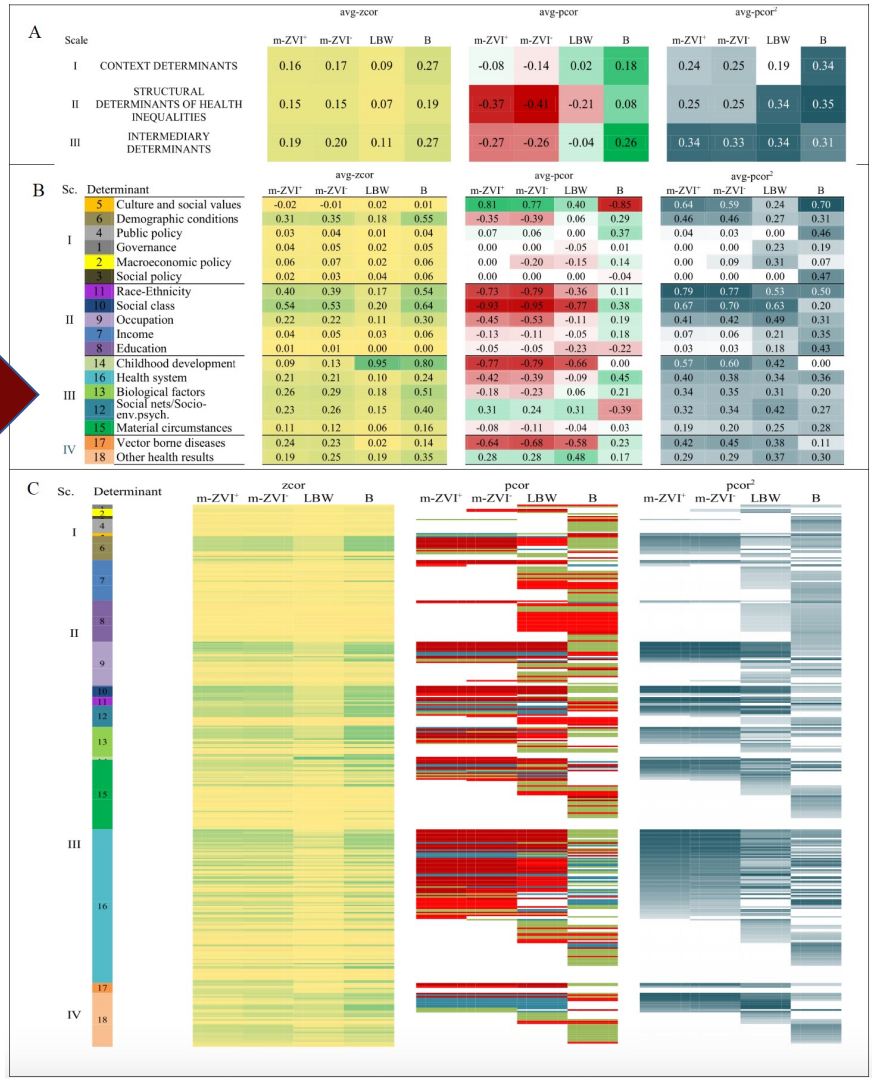


Figure 6. Factors of the intermediary scale.

- These factors convey underlying social stratification of structural factors, by determining differences in exposure and vulnerability to health-compromising conditions and includes material, psychosocial, behavioral, and biological factors. Among the three scales, the intermediary scale contributed the most to the **microcephaly incidence positive for Zika infection** (m-ZIKV⁺) subnetwork (Fig. 4B), and all its factors were associated with that subnetwork.

- 'Childhood development' had the highest avg-pcor² of the factors, mainly due to the value of this factor in the LBW-subnetwork. Similarly, the avg-pcor² of the intermediary scale in the LBW-subnetwork was the highest due to the contributions of all determinants with main roles in the 'undernourishment' node and factors of 'social relationships' and the 'health system.' In the B-subnetwork conversely but as expected, association with problems of 'childhood development' was absent.

- The factor of social relationships includes variables about marital status. Most marital status variables had associations in the m-ZIKV⁺-subnetwork

- These data support the view that different types of family relationships (protective/stable, unstable and/or weak) offer a similar substrate to cases of microcephaly and LBW, but not to cases of normal birth.

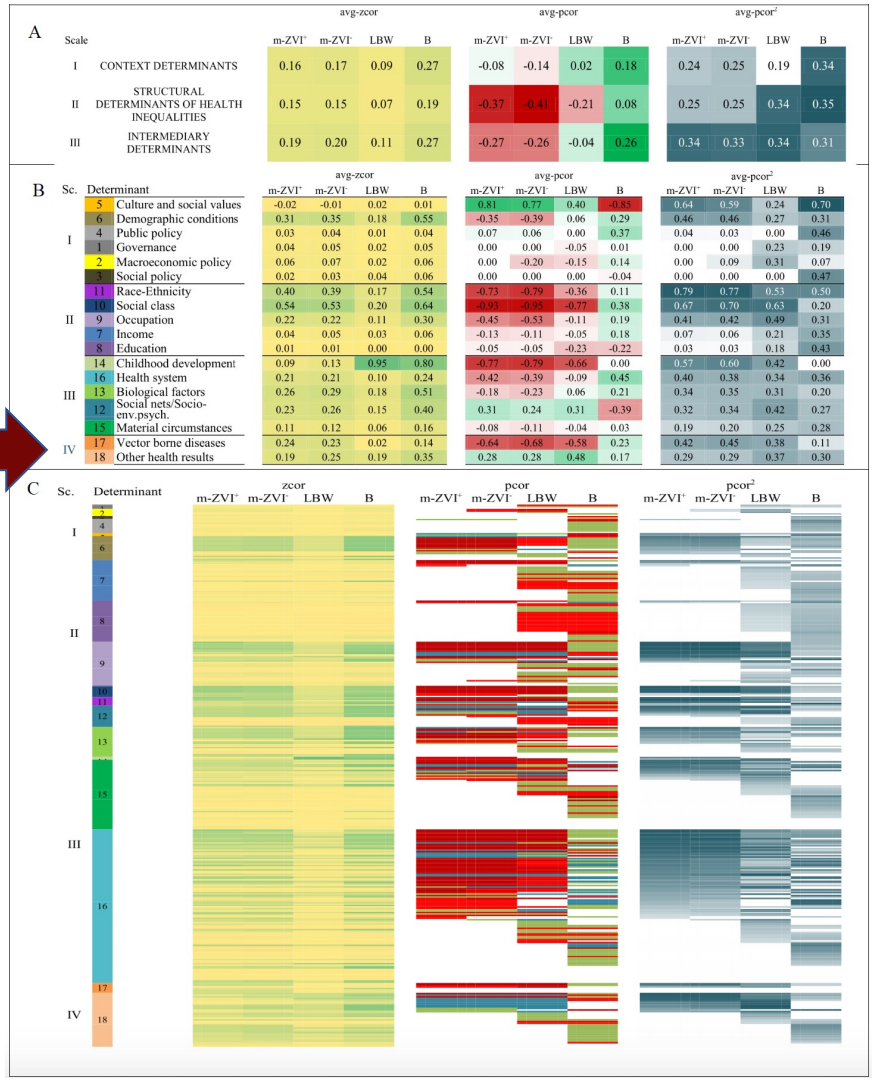
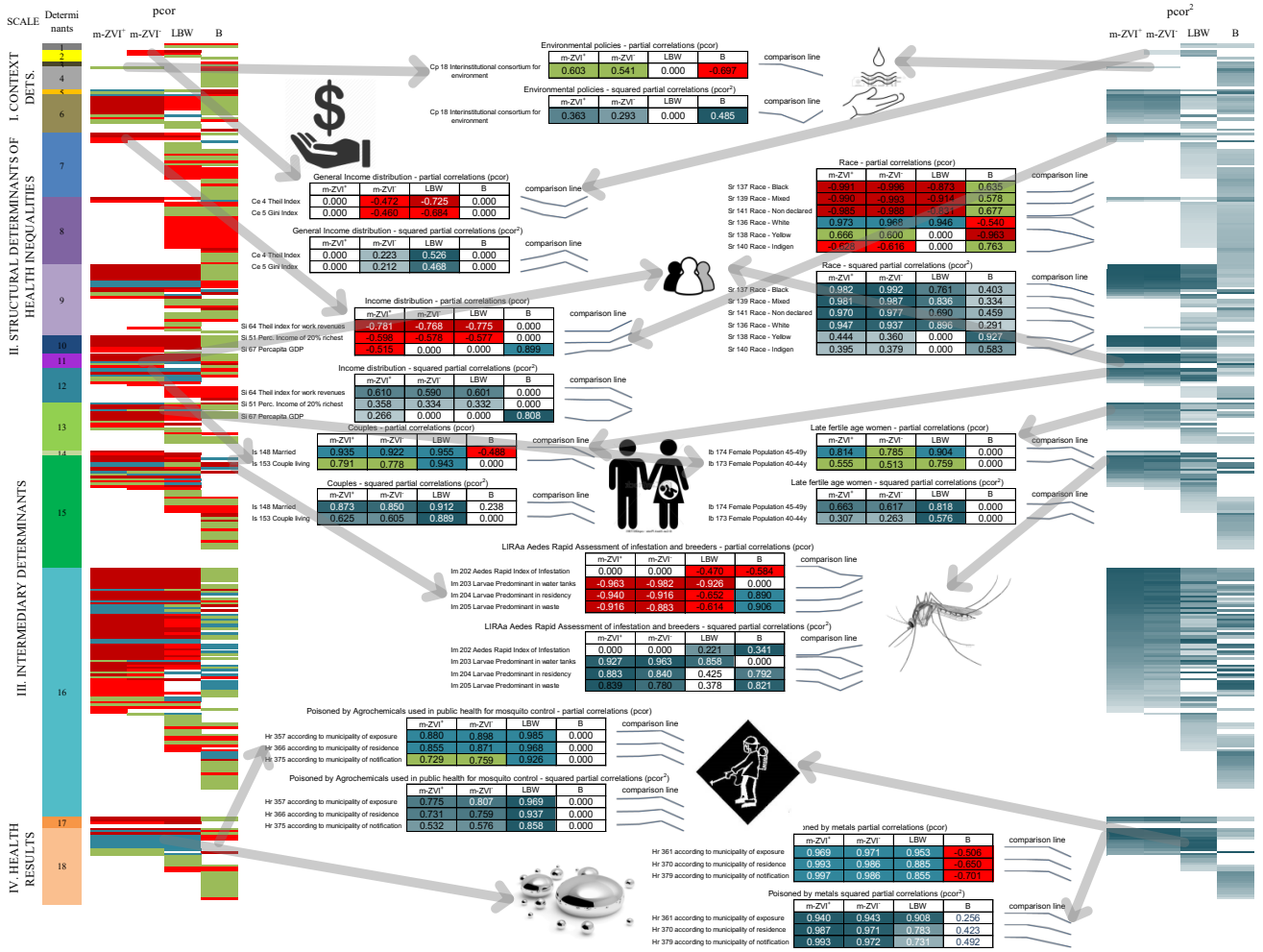


Figure 7. Factors in the scale of the role of health systems in health outcomes.

- Involves access to care and health interventions. This factor had similar avg-pcor^2 in case and control subnetworks, however the opposite sign of avg-pcor in the B-subnetwork that comports with health care having a different role for healthy and ill populations.
- Immunizations are recognized preventive health measures and the focal point w/r re-emergence of infectious diseases that will threaten populations. The (immunity) interventions are not straightforward and encompass diverse results from positive (cross-immunity) to negative (sporadic secondary undesired effects).
- In the control LBW-subnetwork, a wider variety of customary vaccinations during 2015 and 2016 were associated with a with lower pcor^2.
- Broader pattern of vaccinations was present in B-subnetwork with almost all pcor with opposite signs. This grounded the interpretation of other subnetworks and for discerning the potential protective role of vaccinations.
- For other health care interventions, the connection between 'prenatal care' and **microcephaly incidence positive for Zika infection** (m-ZIKV$^+$) was the strongest and pcor^2 successively decreased in the m-ZIKV$^-$-subnetwork to the LBW-subnetwork to the B-subnetwork.

Figure 8. Summary of the Analysis



Environmental Policies common to both types of microcephaly

Differences in Macroecomomic Indicators between both types of microcephaly

Unequal distribution of municipal income between positive and negative m-ZIKV.

Inverse proportional relationship of m-ZIKV+/- in higher income populations.

Differential involvement of white couples and late fertile age women populations showed potential biological vulnerabilities.

There is an associated relationship of ZIKV-related microcephaly with mosquito breeding but not with mosquito populations.

Because these associations are even higher with LBW, this observation should dampen the enthusiasm for the effectiveness of this intervention.

The collective relationships presented for both types of microcephaly is an emergent factor to explain non-ZIKV-related microcephaly.

OVERALL SUMMARY

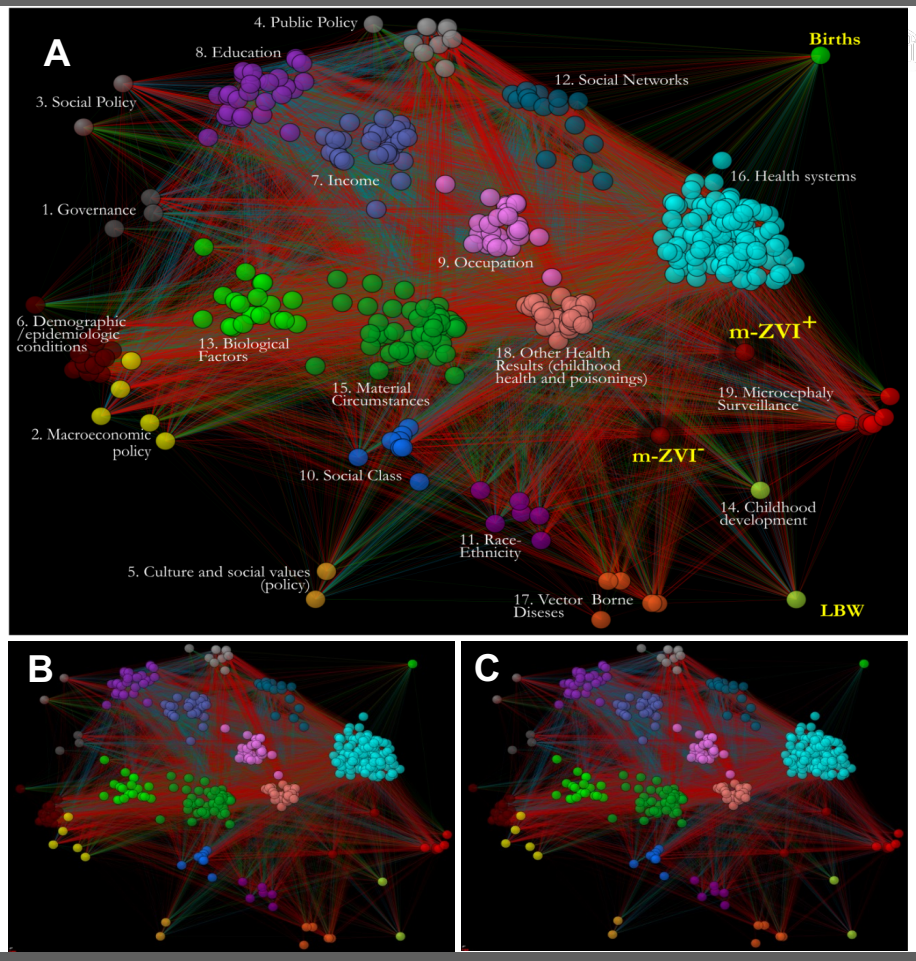
Comparative network inferential analysis of patterns of factors associated with Zika virus infections in Brazil during 2015-2016 coinciding with a microcephaly epidemic identified multiple contributing determinants that advances our understanding of the effects of exposures to chemical and non-chemical stressors in the built, natural, physical, and social environment.

The results revealed latent factors, their central roles and convergence to suggest that effects related to ZIKV-microcephaly incidence in Brazil were not specific to Zika infection and were common to both types of microcephaly.

Diagnostic failure to discern Zika infection during the epidemic likely explains this result. This suggests underestimation of the size of Brazil's $ZIKV^{+}$ microcephaly incidence. Alternatively, assuming that diagnostic uncertainty similarly affected both groups makes evident that microcephaly is a complex event where multiple causes and mediators converge.

Zika diagnostic tests deserve a general inclusion in antenatal screenings, even more, if multiple modes of transmission increase uncertainty about infection risk. Above all, improving diagnostic tests is critical.

Public heath interventions include the spread of agrochemicals to control mosquito populations. An extensive presence of mosquitoes implies widespread exposure to these agrochemicals. Therefore, in addition to the links intuitively found between Zika infection, its vector, and m-$ZIKV^{+}$, a link between the co-occurrence of this nonselective exposure and microcephaly is suggested. These data are in support of molecular data on exposures to the insecticide pyriproxyfen with dampening of neurodevelopmental processes particularly in areas with ZIKV prevalence.



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Thank you!

Twitter reacts to the Bears selection of Justin Fields!

Follow

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@DhoodB

@DhoodB
OSU Buckeye Hood Family: We are elated because we can go see Justin Fields and the Chicago Bears when we are there on weekends during football season.

@DhoodB
We will be visiting our daughter Alexis who is a PGY1 resident at U of Chicago and coupling that to football makes for great weekends in the Windy City!

Ohio State University & Meharry
Paul Juarez
Patricia Cifuentes
M. McCallister
Tongwen Zhang
George Jules
Raina Rhoades
Aramandla Ramesh
Habibeh Khoshbouei
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Nancy Lurie Marks Foundation
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Research Initiative

LITERATURE CITED

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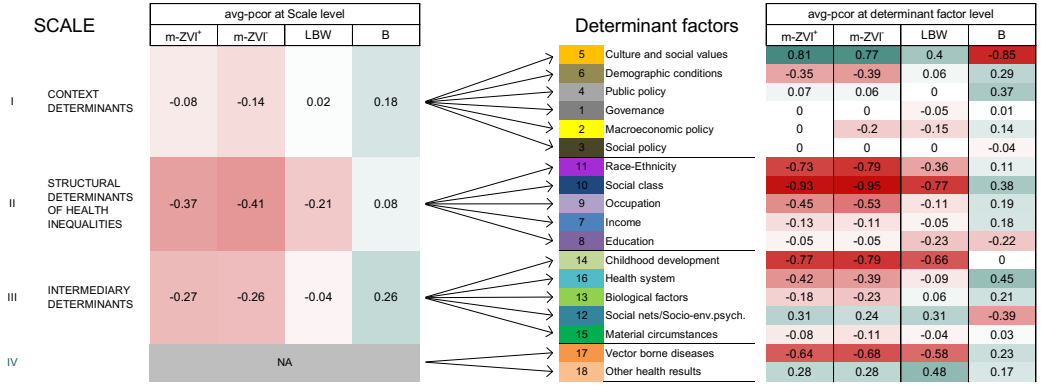
SCALE
avg-pcor at Scale level
m-ZVI+
m-ZVI-
LBW
B
I
CONTEXT DETERMINANTS
-0.08
-0.14
0.02
0.18
II
STRUCTURAL DETERMINANTS OF HEALTH INEQUALITIES
-0.37
-0.41
-0.21
0.08
III
INTERMEDIARY DETERMINANTS
-0.27
-0.26
-0.04
0.26
IV
NA
Determinant factors
5 Culture and social values
6 Demographic conditions
4 Public policy
1 Governance
2 Macroeconomic policy
3 Social policy
11 Race-Ethnicity
10 Social class
9 Occupation
7 Income
8 Education
14 Childhood development
16 Health system
13 Biological factors
12 Social nets/Socio-env.psych.
15 Material circumstances
17 Vector borne diseases
18 Other health results
avg-pcor at determinant factor level
m-ZVI+
m-ZVI-
LBW
B
0.81 0.77 0.4 -0.85
-0.35 -0.39 0.06 0.29
0.07 0.06 0 0.37
0 0 -0.05 0.01
0 -0.2 -0.15 0.14
0 0 0 -0.04
-0.73 -0.79 -0.36 0.11
-0.93 -0.95 -0.77 0.38
-0.45 -0.53 -0.11 0.19
-0.13 -0.11 -0.05 0.18
-0.05 -0.05 -0.23 -0.22
-0.77 -0.79 -0.66 0
-0.42 -0.39 -0.09 0.45
-0.18 -0.23 0.06 0.21
0.31 0.24 0.31 -0.39
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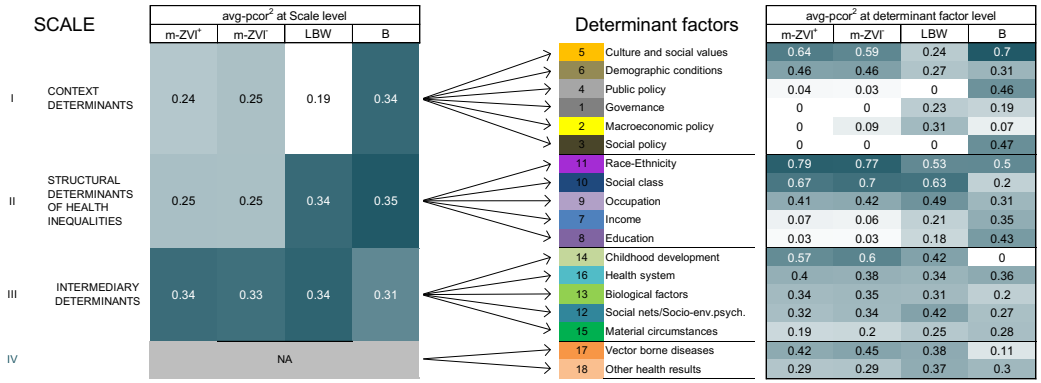
0.28 0.28 0.48 0.17


SCALE
avg-pcor² at Scale level
m-ZVI+
m-ZVI-
LBW
B
I
CONTEXT DETERMINANTS
0.24
0.25
0.19
0.34
II
STRUCTURAL DETERMINANTS OF HEALTH INEQUALITIES
0.25
0.25
0.34
0.35
III
INTERMEDIARY DETERMINANTS
0.34
0.33
0.34
0.31
IV
NA
Determinant factors
5 Culture and social values
6 Demographic conditions
4 Public policy
1 Governance
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11 Race-Ethnicity
10 Social class
9 Occupation
7 Income
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14 Childhood development
16 Health system
13 Biological factors
12 Social nets/Socio-env.psych.
15 Material circumstances
17 Vector borne diseases
18 Other health results
avg-pcor² at determinant factor level
m-ZVI+
m-ZVI-
LBW
B
0.64 0.59 0.24 0.7
0.46 0.46 0.27 0.31
0.04 0.03 0 0.46
0 0 0.23 0.19
0 0.09 0.31 0.07
0 0 0 0.47
0.79 0.77 0.53 0.5
0.67 0.7 0.63 0.2
0.41 0.42 0.49 0.31
0.07 0.06 0.21 0.35
0.03 0.03 0.18 0.43
0.57 0.6 0.42 0
0.4 0.38 0.34 0.36
0.34 0.35 0.31 0.2
0.32 0.34 0.42 0.27
0.19 0.2 0.25 0.28
0.42 0.45 0.38 0.11
0.29 0.29 0.37 0.3