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Do air pollution and neighborhood greenness exposures improve the predicted cardiovascular risk?☆

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ABSTRACT

Background: Numerous studies show associations between exposure to Particulate Matter and Cardiovascular disease (CVD). Current cardiovascular equations incorporate the major risk factors for CVD. The patients' environment, however, is not incorporated in these equations.

Methods: In a retrospective analysis, we assessed the contribution of neighborhood greenness and particulate matter (coarse-PM and PM < 2.5 μm–$PM_{2.5}$) to the development of CVD by analyzing the change in prediction abilities. We included members of the largest health-care provider in Southern-Israel, who had at least one cardiovascular risk factor (dyslipidemia, diabetes, hypertension or smokers). PM exposure and neighborhood greenness (Normalized Difference Vegetation Index-NDVI) were assessed by satellite-based models. We used pooled logistic mixed regressions to obtain the CVD risks including conventional risk factors (i.e. age, gender, blood-pressure, etc.) and measured the model performance with and without PM and NDVI.

Results: We included 23,110 subjects, of whom 12% had CVD. Coarse-PM exposure was associated with stroke and Myocardial-Infarction (MI) (OR 1.02,$p < 0.01$ for both). NDVI was associated with MI: OR 0.72($p < 0.01$) for NDVI 0.1–0.2; and OR 0.52($p = 0.270$) for NDVI > 0.2. The c-statistics slightly improved from 77.30%–77.40% for the prediction of MI ($p = 0.004$) and from 75.60%–75.76% for the prediction of stroke ($p = 0.027$). Calibration was fair in all models. The associations were partially mediated through the patients' comorbidities.

Conclusion: The negligible improvement in the prediction performance, despite significant associations with PM and NDVI, may be due to partial mediation of these associations through the conventional cardiovascular risk factors, suggesting the importance in assessing the environmental effects on more basic physiological pathways when addressing the contribution to the cardiovascular risk.

1. Introduction

Decades ago, the Framingham Heart Study team has published prediction models for the estimation of 10-year risk of developing coronary heart disease (Wilson et al., 1998). Over the years, additional prediction equations and adjustments of the score were developed to improve the models performance in different populations (Conroy et al., 2003; Hippisley-Cox et al., 2007; Ridker et al., 2007).

All risk scores incorporate known predictors proven as risk factors for the development of cardiovascular disease (CVD) (D'Agostino et al., 2008). The most common predictors include age, gender, cholesterol levels, diabetes and smoking status. Yet, beyond these well known clinical factors, there is a plethora of the personal exposures that might influence the CVD risk. Ultimately, the human health is determined by the interaction between the human genome and the environment in its broadest definition (Athersuch and Keun, 2015).

Numerous studies show associations between exposure to Particulate Matter < 10 μm (PM_{10}) and < 2.5 μm in diameter ($PM_{2.5}$) and CVD, usually assessing an increased risk of acute events following the acute increase in exposure (Brook et al., 2004; Mateen and Brook, 2011; Vodonos et al., 2015; Yitshak Sade et al., 2015a, 2015b). Moreover, in recent years, several studies have demonstrated a link between the neighborhood density of the green spaces (e.g. parks) and cardiovascular health (Hu et al., 2008; Pereira et al., 2012). However, the exact pathophysiological pathway question between long term environmental exposure and the development of the disease is not fully

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elucidated. Two models can be proposed, the detrimental effect can either be mediated through the increase in the conventional risk factors burden or be an independent direct effect. In the former model, we can expect an improvement in the discriminatory ability of the cardiovascular prediction models (already accounting for the conventional risk factors) with the inclusion of air pollution exposure when air pollution is properly assessed across space and time.

In this large population study, we aimed to assess the contribution of green space and PM exposure over 10 years to the development of CVD by analyzing the change in prediction abilities of conventional CVD models.

2. Methods

2.1. Study population

This study was approved by the institutional review board of Soroka University Medical Center before data collection. We included adult members of Clalit Health Services (CHS), residing in Southern Israel between the years 2003–2012, who had at least one of the following cardiovascular risk factors: dyslipidemia, diabetes, hypertension or being known smokers. CHS is the largest health care provider in the area, covering approximately 70% of a population of 730,000 residents. The population in South Israel comprises two main ethnic groups: urban Jews (80%) and Bedouin Arabs (20%). The Bedouin-Arabs are predominantly rural and approximately 40% of them reside in temporary housing.

Subjects with no documented address, subject without documented lab results in the follow up period and children (< 18 years) were excluded from the analysis.

The following patient data was obtained from the computerized database of CHS and Soroka University Medical Center (SUMC): age, gender, ethnicity, hospitalizations diagnoses, chronic comorbidities, smoking status, lab results and medications purchases. Socio-economic status (SES) was assigned based on the subjects' home address and stratified according to the definitions of the Central Bureau of Statistics assigning SES level in a scale of one to ten (Central Bureau of Statistics, 2001).

2.2. Study outcomes and risk factors

The study outcomes were identified using the hospitalization diagnoses: acute stroke (ICD9-CM 432–435) and acute myocardial infarction (MI) (ICD9-CM 410). SUMC is the only medical center providing acute neurological and cardiology care in the area; therefore all the patients with acute stroke or MI are referred to SUMC.

The cardiovascular risk factors considered in the analysis were determined a-priory based on the predictors used in the Framingham score (D'Agostino et al., 2008), the southern European score (Conroy et al., 2003) and the American College of Cardiology, American Heart Association equation (Goff et al., 2014). Similar to the original models, our models included age, gender, systolic-blood-pressure (SBP), smoking, lipids status, and diabetes. We added an adjustment for SES and ethnicity.

Diabetes was established in the presence of one of the following: physician confirmed diagnosis, glucose lowering medication purchase, two or more measurement of fasting glucose ≥ 126 mg/dL or HbA1c > 6.5% (American Diabetes Association, 2014). *Dyslipidemia* was established in the presence of one of the following: physician confirmed diagnosis, lipid modifying medication purchase, two or more measurement of low density lipoprotein ≥ 160 mg/dL or total cholesterol > 200 mg/dL. *Arterial hypertension* was established in the presence of one of the following: physician confirmed diagnosis, documented purchase of calcium blockers among patients who are not treated with Verapamil hydrochloride; beta blockers among patients without ischemic heart disease, congestive heart failure or atrial fibrillation; Verapamil hydrochloride, Angiotensin Converting Enzyme inhibitors, thiazides or Angiotensin II receptor blockers among patients without atrial fibrillation; or alpha blockers among patients without a confirmed diagnosis of benign prostate hypertrophy.

The incidence year for the given risk factor was determined as the year of first documented laboratory results, purchase of the relevant medication or physician diagnosis.

All laboratory results, SBP measurements, and smoking status were obtained from physicians visits in the primary clinics. For laboratory results and SBP, part of the subjects had multiple recordings per year and others did not have records of measurements for each follow-up year. Multiple annual recordings were averaged annually. The majority of the subjects (80%) had at least one measurement in the first, second and third quarters of the 10 year study period, and the median proportion of person years with available measurements per subject was 66%. 38% of the person years did not have records of measurements. In the absence of a measurement in a certain year, imputation was made by applying the subject's measurement from the closest available year.

2.3. Environmental data

Southern Israel (Negev) is a desert area, characterized by high levels of PM and frequently subjected to dust storms (Peters et al., 2001), which can increase daily PM_{10} significantly above the 50 mg/m^3 threshold defined by the World Health Organization (Ganor et al., 2010). PM_{10} concentrations during dust storms can reach levels as high as 4200 mg/m^3 (Stafoggia et al., 2008). Semi-arid lands, such as the Negev desert, are characterized by sparse or absence of vegetation cover. However, the land surface is often covered by biological soil crusts (combination of bacteria, fungi, and green algae) which increase NDVI values (Burgheimer et al., 2006). In the Negev, the biological soil crusts have the highest contribution to the overall NDVI signal. The rest of the variation in the signal is due to trees and vegetation cover that changes depending on the season (Schmidt and Karnieli, 2000). In urban areas, where the majority of the population reside, there are trees and bushes maintained by the municipalities.

2.3.1. Air pollution

Coarse PM and $PM_{2.5}$ daily average concentrations were estimated using a hybrid satellite based model incorporating daily satellite remote sensing data and classic land use regression (LUR) methodologies at 1×1 km spatial resolution. In Brief, to estimate PM_{10} and $PM_{2.5}$ concentrations in each grid cell on each day, the AOD-PM relationship was calibrated for each day using data from grid cells with both monitor and AOD values using mixed models with random slopes for day and nested regions in addition to the spatial and temporal predictors such as in a classic LUR. A second model was used to estimate exposures on days when AOD measures were not available (due to cloud coverage, Dust storm days, etc.). The final model was fit with a smooth function of latitude and longitude and a random intercept for each cell (similar to universal kriging) that takes advantage of associations between grid cell AOD values and PM data from monitors located elsewhere, and associations with available AOD values in neighboring grid cells. For more in depth description please refer to Kloog et al., 2015 and Yitshak Sade et al., 2015a, 2015b (Kloog et al., 2015; Yitshak Sade et al., 2015a, 2015b). The model allows us to reliably reconstruct residence levels of air pollution across Israel. Exposure estimates were calculated and assigned for each patient based on their geocoded home address.

2.3.2. Meteorology

Daily data on air temperature and relative humidity for the study period were obtained from the monitoring site located in the center of the largest city in Southern Israel.

2.3.3. Neighborhood greenness

Neighborhood greenness is an ecological exposure that has been

connected to improved health status and associated with multiple health outcomes (Maas et al., 2009; Richardson et al., 2012; Sugiyama et al., 2008). Exposure to green and natural areas around each residential address was estimated using the Normalized Difference Vegetation Index (NDVI). Chlorophyll in plants strongly absorbs visible light (0.4–0.7 μm) for use in photosynthesis, while leaves strongly reflect near-infrared light (0.7–1.1 μm). NDVI calculates the ratio of the difference between the near-infrared region and red reflectance to the sum of these two measures. NDVI was calculated at 30 m area surrounding the residential address using data from the Landsat-8 satellite offered by the U.S. Geological Service (Landsat-8 satellite 2016).

NDVI values typically range from −1 to +1; where values around −1 represent water, values around zero represent bare surfaces (i.e., rocks, sand, houses and roads). Higher NDVI values represent grassland, bush land and green vegetation. South Israel is mostly a desert area and therefore the range of NDVI in the area is limited. We therefore a-priory grouped the NDVI into three groups: values 0–0.1 indicating bare surface, and values 0.1–0.2 and > 0.2 indicating higher levels of vegetative density (Pereira et al., 2012). Using overlay analysis we calculated the mean NDVI value per 30-m pixel for the period 2013–2015, to encompass seasonal variation in greenness levels.

2.4. Statistical analysis

Results are presented by mean ± SD and inter-quartile range (IQR) for continuous variables and as percentages for categorical data. Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC USA).

2.4.1. Model performance

We traced each subject through annual follow-up periods until the year in which they were diagnosed with a major cardiovascular event (stroke or MI) death or the last year of follow-up. Each follow up year was considered as an observation and we used pooled logistic regressions to incorporate the repeated observations for each subject based on his/her number of follow-up years (Dagostino et al., 1990). We used these models to obtain the CVD risks including age, gender, systolic-blood-pressure, high-density-lipoprotein, diabetes, hypertension, ethnicity, smoking, SES and dyslipidemia as covariates. We considered the aforementioned model as the basic model and assessed the cardiovascular risk by using logistic mixed models. We then added exposure to PM and NDVI to the basic model and assessed the change in model performance.

Discrimination ability was assessed by the area under the receiver-operating-characteristic curve (c-statistics), net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (Pencina et al., 2008b). NRI is based on a correct reclassification of predicted risks of subjects with and without events using a new prediction model over another model. We used the category free NRI, in which any movement upwards in probabilities of events or movement downwards in probabilities of non-events counts as an up or down movement (Pencina et al., 2008a). The overall NRI estimate ranges between −2 and 2 and is the sum of the net percentages of subjects who were correctly assigned with a different predicted risk (Leening et al., 2014). The IDI is a measure of the model's improvement in terms of average sensitivity and specificity (a measure of how far apart on average they are). We used the relative IDI, defined as the ratio of IDI over the discrimination slope of the basic model (Pencina et al., 2008a).

Calibration was assessed by the Hosmer Lemenshow statistics for goodness-of-fit. We used the regression coefficients from the full model to calculate the predicted probability of each cardiovascular event for each patient. The probabilities were divided by deciles of outcomes probabilities and for each decile, we reported the observed MI or stroke rate. We graphically represented the observed and expected rates by deciles and calculated the standardized incidence index for each decile (equal to the observed rates divided by the average expected rates). Effect estimates are presented as odds ratios (OR) and 95% confidence intervals (CI).

2.4.2. Mediation analysis

We used a method proposed by Baron and Kenny (Baron and Kenny, 1986)to assess potential mediation of the effect of PM and NDVI, through the other clinical characteristics. Specifically, we utilized the following three steps: *Model 1: Y = X; Model 2: M = X; Model 3: Y = X + M.* Where X is the independent variable (PM or NDVI), M is the mediator (diabetes, dyslipidemia or hypertension) and Y is the outcome (stroke or MI). In case of complete mediation, a significant association will be observed in the first two models, but not in the X-Y association in the third model. If only the first two steps are met, partial mediation may still be present. To assess the indirect effects of PM and NDVI, and whether they are partially mediated through the patient's clinical characteristics, we utilized the Sobel (Sobel, 1982), Goodman and Aroian tests (Goodman, 1960). The null hypothesis in these three tests is that the coefficient of the indirect effect equals zero. The test statistic is computed by dividing the indirect effect coefficient by three versions of standard error suggested by Sobel, Goodman and Aroian and significant test results suggest that partial mediation is present (Goodman, 1960; Sobel, 1982).

3. Results

3.1. Study population

We included 23,110 subjects with at least one known cardiovascular risk factor: 32% were smokers, 38% had diabetes, 82% hypertension and 78% dyslipidemia. Of the included subjects 12% had a cardiovascular event (6.7% MI and 6.1% ischemic stroke). Overall, the calculated cardiovascular risk scores were higher among subjects who had an event (Table 1).

3.2. Environmental exposures

The average annual temperature was 19.8 °C, with maximal annual temperatures of 33 °C recorded during the study period. The NDVI

Table 1
Population characteristics.

Population characteristics	Severe cardiovascular event		*P* value
	Yes 11.9% (2739)	No 88.1% (20,371)	
Age, Mean ± SD	65.5 ± 13.2	72.5 ± 11.8	< 0.001
Male gender, %(n)	41.6 (8475)	57.3 (1571)	< 0.001
Smoking status, %(n)	31.4 (6404)	39.8 (1090)	< 0.001
Comorbidities, %(n)			
Diabetes	35.1 (7146)	58.2 (1594)	< 0.001
Hypertension	80.3 (16,345)	94.5 (2588)	< 0.001
Dyslipidemia	76.9 (15,672)	92.5 (2533)	< 0.001
CHD	11.5 (2351)	71.6 (1962)	
Measurements, %(n)			
LDL, Mean ± SD	118.3 ± 27.4	112.0 ± 27.4	< 0.001
HDL, Mean ± SD	51.2 ± 12.0	48.0 ± 11.4	< 0.001
SBP, Mean ± SD	132.0 ± 13.5	137.0 ± 13.5	< 0.001
Cardiovascular outcome, %(n)			
MI		57.3 (1570)	
Stroke		51.7 (1416)	
Cardiovascular risk, Median (IQR)			
Framingham[a]	17% (9%; 30%)	31% (19%; 47%)	< 0.001
SCORE[b]	7% (2%; 16%)	15% (7%; 26%)	< 0.001
ACC/AHA[c]	5% (2%; 12%)	13% (7%; 21%)	< 0.001

[a] The Framingham Cardiovascular Risk predicts coronary heart diseases, stroke, congestive heart failure or peripheral arterial disease).
[b] The Southern European Score predicts cardiac death.
[c] The ACC/AHA score predicts cardiac death or severe cardiovascular event.

Table 2
Summary statistics of air pollution and meteorological parameters.

Parameter	Mean ± SD	IQR	MAX
Coarse PM (μg/m^3)	30.60 ± 4.81	27.24–33.63	43.35
$PM_{2.5}$ (μg/m^3)	22.10 ± 1.78	20.84–23.21	29.20
NDVI	0.17 ± 0.06	0.13–0.21	0.55
Temperature, °C	19.86 ± 0.66	19.61–19.88	21.68
Relative humidity, %	66.52 ± 6.16	59.82–72.17	75.35

$PM_{2.5}$ = Particulate Matter < 2.5 μm; NDVI = Normalized Difference Vegetation Index; SD = standard deviation; IQR = inter quartile range; MAX = maximal value.

values ranged between 0.13 and 0.21. Higher NDVI values were observed in Jewish localities (mean 0.18) compared to Bedouin localities (mean 0.13, $p < 0.001$). No differences in NDVI values were observed between rural and urban localities. The annual coarse PM and $PM_{2.5}$ average concentrations were 30.60 μg/m^3 and 22.18 μg/m^3, respectively, reaching maximal concentrations of 43.35 μg/m^3 and 29.27 μg/m^3, respectively (Table 2). The correlation between all three exposures was low: $r = 0.15$ ($p < 0.01$) for course PM and $PM_{2.5}$, $r = 0.07$ ($p < 0.01$) for course PM and NDVI and $r = 0.13$ ($p < 0.01$) for $PM_{2.5}$ and NDVI.

3.3. Single exposure models

We utilized single exposure pooled logistic regressions using mixed models to assess the association between MI or stroke and coarse PM, $PM_{2.5}$ and NDVI separately.

3.3.1. Air pollution

Annual coarse PM exposure was associated with stroke (OR 1.02, 95%CI 1.01; 1.03) and MI (OR 1.02, 95%CI 1.00; 1.03). Annual $PM_{2.5}$ exposure was negatively associated with MI (OR 0.92, 95% CI 0.90; 0.95), but not associated with ischemic stroke (OR 0.99, 95% CI 0.96; 1.02) (Table 3).

3.3.2. NDVI

In the prediction of MI we observed a dose response relationship with NDVI, showing stronger protective associations with greener areas: OR 0.72 (95%CI 0.61; 0.85) for NDVI values between 0.1 and 0.2; and OR 0.52 (95% CI 0.19; 1.69) for NDVI values > 0.2. No association was observed between stroke and NDVI (Table 3). Supplementary Table 1 shows the characteristics of the population by the amount of neighborhood greenness. Among subjects who had less green space in their house surroundings (NDVI 0–0.1) the median SES was lower, the mean age was higher, Bedouin descent was more frequent and all cardiovascular risk factors were more frequent. Lastly, subjects who resided in greener places were exposed to higher concentrations of coarse PM (annual average of 30.7 μg/m^3) compared to the other group (annual average of 28.7 μg/m^3) (Supplementary Table 1).

Table 3
The association between PM, neighborhood greenness and cardiovascular outcomes.

	MI			
Parameter	[a]OR (95% CI)	*P* value	[b]OR (95% CI)	*P* value
$PM_{2.5}$	0.93 (0.90;0.96)	< 0.01	0.92 (0.90;0.95)	< 0.001
Course PM	1.01 (1.00;1.02)	0.043	1.02 (1.00;1.03)	< 0.001
NDVI				
0–0.1	Reference group		Reference group	
0.1–0.2	0.72 (0.33;0.70)	< 0.01	0.72 (0.61;0.85)	< 0.01
0.2 +	0.52 (0.19;2.63)	0.238	0.57 (0.19;1.69)	0.318
	Stroke			
Parameter	OR (95% CI)	*P* value	OR (95% CI)	*P* value
$PM_{2.5}$	0.99 (0.96;1.02)	0.774	0.98 (0.95;1.01)	0.216
Course PM	1.02 (1.01;1.03)	< 0.01	1.02 (1.01;1.03)	< 0.01
NDVI				
0–0.1	Reference group		Reference group	
0.1–0.2	0.92 (0.53;1.25)	0.406	0.88 (0.72;1.06)	0.200
0.2 +	1.53 (0.50;14.40)	0.252	1.54 (0.74;3.22)	0.244

Table 3 shows the results of the association between green space, course PM and stroke or myocardial infarction (MI). The models were adjusted for age, gender, systolic-blood-pressure, high-density-lipoprotein, diabetes, hypertension, ethnicity, smoking, SES and dyslipidemia.

$PM_{2.5}$ = Particulate Matter < 2.5 μm; NDVI = Normalized Difference Vegetation Index.

[a] Single exposure models including Course PM, $PM_{2.5}$ and NDVI separately.

[b] Multipollutant models including all three exposures.

3.4. The adjusted association between PM, green space and cardiovascular events

The effect estimates of the associations between the cardiovascular events and PM or NDVI did not change in the multiple-exposures model. Coarse PM remained significantly associated with MI and stroke, $PM_{2.5}$ and NDVI remained significantly associated with MI. Adjustment for temperature did not change the results (Table 3).

3.5. Discrimination

For the prediction of MI, the change in c-statistics was significant ($p = 0.004$) despite a small improvement from 77.30% in the basic model (inclusive of age, gender, SES ethnicity, smoking, systolic blood pressure, high-density-lipoprotein levels, diabetes, hypertension, ethnicity and dyslipidemia) to 77.50% in the new model comprising NDVI, coarse PM and $PM_{2.5}$ as well. The NRI showed significant improvement in the new model, over the basic model (NRI 0.15, $p < 0.01$). The integrated difference in average sensitivity and specificity differed by 5.3% ($p < 0.01$) between the basic and the new model.

Similar to MI, for the prediction of stroke, the improvement in c-statistics was significant but minor (from 75.60% in the basic model to 75.80% in the new model). NRI measures showed slight improvement in discrimination and the integrated difference in average sensitivity and specificity differed by 2.8% ($p = 0.001$) between the basic and the new model (Table 4).The change in the discriminatory ability for the MI models was better among females and among older patients. The change in the discriminatory ability for the stroke models was better among males and among older patients. For both outcomes, the model performance among subjects of higher and lower SES was similar (Supplementary Tables 2 and 3).

Table 4
Performance of risk prediction models with or without PM and VNDI as predictors.

Performance measure	MI	Stroke
Discrimination		
c-statistics: model1[a]	77.30%	75.60%
c-statistics: model 2[b]	77.50%	75.80%
p value for the difference in c-statistics	0.004	0.027
Calibration		
^{3}H-L test		
x^2(*p* value): model 1	43.6 (< 0.01)	29.3 (< 0.01)
x^2(*p* value): model 2	41.1 (< 0.01)	27.7 (< 0.01)
Reclassification		
NRI (*p* value)	0.15 (< 0.01)	0.10 (< 0.01)
Net of events reclassified correctly (*p* value)	10% (< 0.01)	7% (< 0.01)
Net of non-events reclassified correctly (*p* value)	6% (< 0.01)	3% (< 0.01)
Relative IDI (*p* value)	5.3% (< 0.01)	2.8% (0.001)

H-L = Hosmer Lemenshow; NRI = Net reclassification improvement (category free); IDI = Integrated discrimination improvement.

[a] Model 1: age, socioeconomic status, gender, comorbidities (diabetes, hypertension, and dyslipidemia), smoking status SBP and HDL levels.

[b] Model 2: model 1 + NDVI, course PM and $PM_{2.5}$.

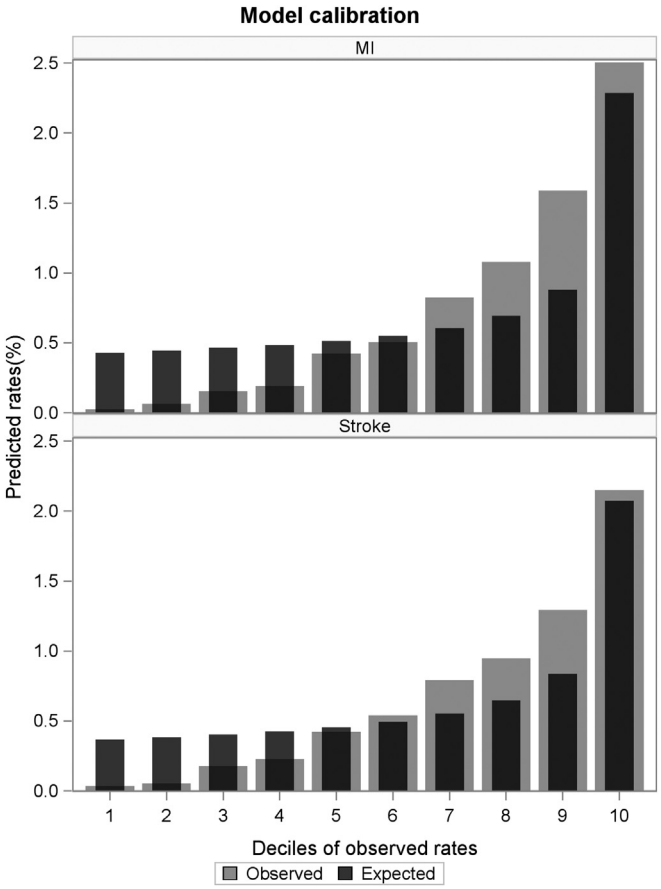

Fig. 1. Calibration of the fully adjusted models for the prediction of stroke and MI (including age, socioeconomic status, gender, diabetes, hypertension, dyslipidemia, smoking status, SBP and HDL levels, NDVI, $PM_{2.5}$ and coarse PM).

3.6. Calibration

The difference between the expected and observed rates of MI and stroke was minimal across all the risk deciles (Supplementary Table 4). We observed an overestimation of the predicted risk in the lower deciles and underestimation of the risk in the upper deciles. Results were similar in the stroke prediction model. The models calibration was better among males and older patients (Supplementary Figs. 1 and 2). Given a large sample size of over 215,000 person years, despite similar observed and expected rates in the models, which suggests good calibration; the differences between the rates was significant in all models (Table 4 and Fig. 1).

3.7. Mediation analysis

Since coarse PM was associated with stroke and MI but did not improve the model performance, we sought to investigate whether these associations are mediated through other clinical characteristics in the model. Coarse PM was significantly associated with dyslipidemia, hypertension and diabetes, but the association with coarse PM did not change with the inclusion of these covariates in the model, suggesting the absence of complete mediation. The significant Sobel, Goodman and Aroian tests however suggests that the association with coarse PM is partially mediated through these clinical parameters (Supplementary Table 5.a and 5.b). The same method was applied to assess the mediation of the association between NDVI and MI. Similarly, no complete mediation was present, but the tests for partial mediation supported an indirect effect through dyslipidemia and diabetes (Supplementary Table 5.c).

4. Discussion

In this study, we found a significant increased risk for stroke and MI, associated with a higher chronic exposure to coarse PM and a decreased MI risk associated with larger amount of neighborhood greenness. The incorporation of PM and NDVI in the prediction of stroke and MI, in addition to the conventional risk factors, only minimally improved the c statistics and did not yield clinically relevant improvement in the NRI and IDI measures, possibly due to partial mediation through the patients' morbidities.

It is well established that genome-wide association studies alone cannot fully predict individual disease risk (Wild, 2012). The disease risk incorporates the lifelong history of all environmental ("non-genetic") exposures, complementing the genome and remodeling the individual's epigenetic terrain (Ho et al., 2012; Wild, 2012). Numerous studies dedicated to the clinical cardiovascular scores attributed the variation found in the scores prediction abilities to the characteristics of the assessed populations (D'Agostino et al., 2001; Ducimetiere et al., 1980; Menotti et al., 2000), which might also be related to the variations in the environmental exposure characteristics over time and different geographical areas. Yet, unlike the well-established risk factors, the patients' environmental exposures are not routinely incorporated in the cardiovascular risk scores available to date (Conroy et al., 2003; D'Agostino et al., 2008).

Greenhouse gas emissions generated by human activity and anthropogenic air pollution are changing the global climate (McMichael et al., 2006) and may negatively affect human health. The ongoing climate change is attributed to population growth, increased consumption and urbanization (Satterthwaite, 2009).The increasing surface of built environment, transportation systems and infrastructure affects human health directly through air pollution exposure, and indirectly through forcing a sedentary lifestyle. Limited access to green space (Younger et al., 2008), associated with decline in well-being (Coutts et al., 2010), mental health (de Vries et al., 2003), increased stress, decreased longevity (Sugiyama et al., 2008) and detrimental life style (Nielsen and Hansen, 2007) contributes to the health risks.

The association between acute cardiovascular events and environmental exposure has been described previously. Pollutants as triggers for an acute event are hypothesized to work through activated inflammation leading to the prothrombotic states (Goff et al., 2014; Yitshak Sade et al., 2015a, 2015b; Vodonos et al., 2015; Yitshak Sade et al., 2016; Yitshak Sade et al., 2015a, 2015b; Yitshak Sade et al., 2014). In the current study we attempted to show that longer more chronic exposure is associated with an increasing risk of the cardiovascular events. Two potential pathophysiological pathways for such an association can be proposed: (1) the increased risk associated with pollution is due to the direct effect on the cardiovascular system (e.g. building of a vulnerable plaque) and; (2) pollutions effect is mediated through the effect on the common clinical risk factors (e.g. glucose levels etc). In case of a direct effect we can expect an improvement of the cardiovascular models abilities to predict the outcomes, while in the case of indirect effect models already accounting for the common risk factors should remain unchanged.

In the prediction of stroke, we observed an increased risk for stroke associated with exposure to higher concentrations of coarse PM, but the improvement in the model performance with the inclusion of the environmental exposures was negligible. As shown in the previous studies, PM_{10} and $PM_{2.5}$exposures are associated with lipids (Chuang et al., 2010), glucose (Chuang et al., 2010; Yitshak Sade et al., 2015a, 2015b) and blood pressure (Chuang et al., 2010). Hence, it is possible that the association between air pollution and stroke is mediated through these factors, and therefore does not contribute independently to the model prediction. The mediation analysis, which showed partial mediation through the association with dyslipidemia, hypertension and diabetes, supports this theory.

Our findings showed lower risk of MI in greener areas. Several

researchers attempted to investigate the underlying mechanism explaining the beneficial effect of green environment on health suggested that it involves the beneficial role of physical activity (Richardson et al., 2012), healthier lifestyle (Lachowycz and Jones, 2011) and reduced stress (Sugiyama et al., 2008). We found that this association was partially mediated through the associations with dyslipidemia and diabetes.

In age stratified models, the improvement in models performance with the inclusion of the environmental exposures was slightly better among older patients. Several studies found older patients to be more susceptible to the air pollution effect (Samoli et al., 2008; Zanobetti and Schwartz, 2002). It is possible that the higher susceptibility to PM yielded better model performance with the inclusion of PM among this population. For gender, the model performance for the prediction of MI was better among females and the model performance for the prediction of stroke was better for males. There is a growing evidence of modifications of the PM effects by gender, but the literature is inconsistent. Gender differences of the PM effect may be due to different activity patterns, biological differences and different characteristics of target organs and hormonal systemic regulation (Clougherty, 2010).

Our study had several limitations. First, the inclusion of susceptible population limits the generalizability of our findings. Also, since the study relied on routinely collected data, clinical measurements were not available for all follow up years. However, the majority of the subjects had available data for at least one follow up year during the first, second and third quartiles of the study period and missing data was imputed. Second, cardiovascular diseases were reported to be associated with other environmental exposures such as noise (Stansfeld and Matheson, 2003; Vandasova et al., 2016), physical activity (Warburton et al., 2006) and walkability (Muller-Riemenschneider et al., 2013). We had no available data regarding and the aforementioned exposures; therefore we could not incorporate a wide range of environmental exposures in the prediction models. In addition, similar to other studies assessing environmental exposures; measurement error in the estimated exposure to air pollution is a possible limitation of our study. Due to our use of novel, spatially and temporally resolved satellite models to estimate individual exposure to PM at the residential address, the error is expected to be minor. However, since we did not have information regarding the residential history of the study population, exposure measurement error may still be present. Lastly, the protective effect of $PM_{2.5}$ found in our study may be due to residual confounding caused by unmeasured confounders.

In conclusion, we found an association between neighborhood greenness and the risk of MI and an association between coarse PM and the risk of MI and stroke, which are partially mediated through the conventional cardiovascular risk factors. Considering the broad extent of exposed population and the continuous nature of exposure, even small effects may have significance to public health (Kunzli et al., 2000; Rajagopalan and Brook, 2012).

The human health is affected by the interaction between the human genome and the environment, and it is therefore important to further investigate the contribution of incorporating the patients' environmental exposures in the risk equations which for the primary care physicians' ability to assess the individual patient's risk of developing CVD. Our results supports the importance in assessing the effect of air pollution on more basic physiological pathways (such as glucose and lipids metabolism) when addressing the contribution of environmental exposures to the development of cardiovascular risk.

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