Supplementary text

Online-only text

Methods – Sample

In the Normative Aging Study, after a participant scheduled his visit, about a month before the visit, he was mailed the BSI assessment survey along with the many others. Most of the participants did the assessment in advance of the visit (generally only a few days before) and brought them with them and some of them did the surveys at the visit. However, there were some who did not put a date on the survey and the VA staff instead assigned the date of the visit for the assessment. Other covariates information, such as blood measures, medication use, physical exams and other demographical variables were still collected at the study visits. In this specific analysis, we utilized those study visits that successfully collected information on BSI assessment over the study period of 2000-2014.

Methods –Statistical Analysis *(discussion on the confounding structure as provided in eFigure 1)*

Based on the DAG shown in **eFigure 1**, in detail, when deciding the list of covariates to adjust for to study the associations between ambient air pollution and individual level psychiatric symptoms, we need to think from the following covariates sets.

1) **Area level neighborhood characteristics** (such as census tract population density, median household income and median house value), **calendar year, season, ambient co-exposures** (such as other pollutants, temperature and relative humidity) are the key confounders that relate with ambient exposures and the outcomes (psychiatric symptom measurements) since we are studying area-level ambient exposures instead of personal exposure levels in this study.

2) We still adjust for the **conventional demographical factors** (such as age, race, education, marital status) and **BMI** in that they could be risk factors for the psychiatric health status only and do not sit in the middle of the causal pathway from our exposure to outcome. Therefore, by controlling for them, we have more stabilized and precise effect estimation.
3) We removed all the **physical health conditions** that are possibly **mediators** in the causal pathway from the air pollution exposures to the symptoms scores. Controlling for them would result in a direct effect of ambient air pollution on the outcomes instead of a total effect.
4) We still kept the **key area-level contextual variables** because evidence has shown that they are the biggest confounders in air pollution epidemiology.(Sheppard et al. 2012) And this is one improvement of our paper compared with previous papers.
5) **Psychiatric medication use** could be a potential mediator from ambient exposures to the psychiatric symptoms, or it could be a downstream collider if it instead is a downstream consequence of having abnormal psychiatric symptoms and affected by harmful ambient exposures. Therefore, to address this, we removed people on medication use in the study population and were careful about the adjustment for this variable in the analysis.
6) Another interesting covariate set to think about is the role of some **behavioral factors** that correlate with mental health conditions. First, we have information on smoking, drinking and physical activity level at each visit. However, if they are covariates that happen before the occurrence of symptoms and influence the symptoms, they are similar to the adjustment of demographical factors, such as age, race, etc. to make the estimation more stable. Thus, we can additionally adjust for them in the models. But if they instead are downstream consequences of having psychiatric problems as indicated by elevated levels psychiatric symptoms, i.e. people with poor mental health conditions tend to be less active, stay at home, or self-medicate with alcohol or tobacco (Scott and Happell 2011), controlling for them would lead to selection bias if they are also correlated with our exposures. Therefore, in the

formal analysis, although we presented the results based on two sets of adjustment (one includes behavioral factors, one not), we wanted to ask for caution when interpreting the related results when adjusting for the behavioral factors.

Results – Global Scores

It was not quite straight forward to find a good community reference sample we could use to compute the T scores for the particular Normative Aging Study (NAS) participants we have. The NAS sample we have is a group of American older men with >95% being whites and most of them veterans. What we used was instead all the participants we have in the NAS dataset with sufficient information on BSI records (>=41 items answered) at their baseline visit (n=1177). We also tested the likely bias we can have for effect estimates reported on T scores if we used different community reference samples, such as the **Derogatis non-patient reference sample,** which consists of 719 non-psychiatric patient persons with approximately 1:1 male: female ratio and a median age of 46.0 yrs. It is the community normal sample presented along with the introduction of BSI measure in 1983 by Dr. Derogatis and coauthors. However, we think it would not be that ideal to use this in the main analysis since the reference sample here is mixing male and female and has an average age much younger than our sample. We also tried to test the possible bias if we instead used the remaining NAS individuals (n=607) with sufficient information on BSI but did not enter our study eventually as the **NAS 607 reference sample**. We applied their baseline visit scores to inform a NAS study community reference sample. However, this group of people includes individuals on psychiatric medication use who very much likely could be psychiatric patients that differed from our study sample (relatively healthy (veteran) men with no psych medication use). To allow comparison, we repeated the main analysis looking at different time windows of exposures and GSI/PSDI T scores and observed similar T score effect estimates using **Derogatis non-patient reference sample** and the **NAS 607 reference sample** to what we reported in the main text (**eTable 2**).

eTable 1. Brief Symptom Inventory Positive Symptom Distress Index (PSDI) T Score, Global Severity Index (GSI) T Score and Positive Symptom Total (PST) Difference (with 95% Confidence Interval, CI) per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3) In Normative Aging Study, 2000-2014. (Single-Pollutant Model)

Exposure	Window	Estimate [a] (95% CI)	Estimate [a] (95% CI)	Estimate [a] (95% CI)
		PSDI T Score [b]	GSI T Score [b]	PST [b]
NO_2	1Wk	1.26 (0.06, 2.47)	0.20 (-0.88, 1.28)	-0.12 (-1.08, 0.84)
	4Wk	1.24 (-0.13, 2.62)	0.37 (-0.87, 1.60)	0.08 (-1.02, 1.18)
	8Wk	1.24 (-0.20, 2.67)	0.47 (-0.80, 1.73)	0.18 (-0.95, 1.32)
	1Yr	0.56 (-0.89, 2.01)	-0.58 (-1.87, 0.71)	-0.19 (-1.37, 0.99)
O_3	1Wk	1.33 (0.46, 2.20)	0.28 (-0.54, 1.09)	-0.19 (-0.90, 0.52)
	4Wk	0.97 (0.02, 1.93)	0.03 (-0.86, 0.93)	-0.25 (-1.04, 0.53)
	8Wk	0.54 (-0.46, 1.53)	-0.16 (-1.08, 0.76)	-0.23 (-1.03, 0.58)
	1Yr	0.63 (-0.57, 1.84)	0.47 (-0.61, 1.55)	-0.09 (-1.06, 0.87)
$PM_{2.5}$	1Wk	0.13 (-0.54, 0.80)	-0.07 (-0.69, 0.55)	-0.28 (-0.83, 0.27)
	4Wk	0.39 (-0.52, 1.29)	0.17 (-0.66, 0.99)	-0.09 (-0.82, 0.64)
	8Wk	0.66 (-0.31, 1.62)	0.30 (-0.55, 1.15)	0.05 (-0.70, 0.80)
	1Yr	-0.71 (-2.33, 0.91)	-0.21 (-1.71, 1.28)	-0.27 (-1.61, 1.08)

Annotation: [a] Difference in the scores per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3);
[b] Adjusted for calendar year, age, bmi, race, education, marital status, season, census tract median household income, census tract median value of house, census tract population density. 1Wk, 4Wk, 8Wk and 1Yr means for the exposure windows of average 1 week, 4 weeks, 8 weeks and one year prior to the visit date.

eTable 2. Brief Symptom Inventory Positive Symptom Distress Index (PSDI) and Global Severity Index (GSI) T Score Difference (with 95% Confidence Interval, CI) per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3) In Normative Aging Study, 2000-2014. (Multi-Pollutant Model, Using Different Community Reference Sample to Create T Score)

		Derogatis Non-patient Reference		NAS 607 Reference (Baseline)	
Exposure	**Window**	**Estimate [a] (95% CI)**	**Estimate [a] (95% CI)**	**Estimate [a] (95% CI)**	**Estimate [a] (95% CI)**
		GSI T Score [b]	**PSDI T Score [b]**	**GSI T Score [b]**	**PSDI T Score [b]**
NO_2	1Wk	0.43 (-0.79, 1.66)	1.36 (0.26, 2.46)	0.40 (-0.72, 1.51)	1.70 (0.33, 3.07)
	4Wk	0.51 (-0.94, 1.95)	1.45 (0.16, 2.75)	0.46 (-0.85, 1.78)	1.82 (0.20, 3.44)
	8Wk	0.36 (-1.14, 1.86)	1.29 (-0.07, 2.65)	0.33 (-1.04, 1.70)	1.61 (-0.09, 3.31)
	1Yr	-0.42 (-1.96, 1.11)	1.18 (-0.23, 2.59)	-0.39 (-1.79, 1.01)	1.47 (-0.29, 3.24)
O_3	1Wk	0.26 (-0.71, 1.24)	1.41 (0.57, 2.25)	0.24 (-0.65, 1.13)	1.77 (0.72, 2.81)
	4Wk	-0.09 (-1.20, 1.02)	1.15 (0.19, 2.11)	-0.08 (-1.10, 0.93)	1.44 (0.24, 2.64)
	8Wk	-0.14 (-1.31, 1.02)	0.77 (-0.23, 1.78)	-0.13 (-1.19, 0.93)	0.97 (-0.29, 2.23)
	1Yr	0.38 (-0.87, 1.62)	0.88 (-0.27, 2.03)	0.34 (-0.79, 1.48)	1.11 (-0.33, 2.54)
$PM_{2.5}$	1Wk	-0.26 (-1.00, 0.48)	-0.46 (-1.10, 0.18)	-0.24 (-0.91, 0.44)	-0.57 (-1.37, 0.23)
	4Wk	0.07 (-0.86, 1.01)	-0.13 (-0.97, 0.70)	0.07 (-0.79, 0.92)	-0.17 (-1.21, 0.88)
	8Wk	0.30 (-0.64, 1.24)	0.29 (-0.57, 1.15)	0.27 (-0.59, 1.13)	0.36 (-0.72, 1.43)
	1Yr	-0.14 (-1.81, 1.52)	-0.85 (-2.32, 0.63)	-0.13 (-1.65, 1.39)	-1.06 (-2.90, 0.78)

Annotation: [a] Difference in the T scores per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3);
[b] Adjusted for co-exposures, temperature (except for 1 Yr window), relative humidity, calendar year, age, bmi, race, education, marital status, season, census tract median household income, census tract median value of house, census tract population density. 1Wk, 4Wk, 8Wk and 1Yr means for the exposure windows of average 1 week, 4 weeks, 8 weeks and one year prior to the visit date. Derogatis non-patient reference sample consists of 719 non-psychiatric patient persons with approximately 1:1 male : female ratio and a median age of 46.0 yrs, it is the community normal sample presented along with the introduction of BSI measure in 1983 by Dr. Derogatis and coauthors. NAS 607 reference sample consists of the 607 BSI participants among our Normative Aging Study sample excluding the 570 individuals who entered this study. We applied their baseline visit scores to inform a NAS study community reference sample.

eTable 3. Brief Symptom Inventory Positive Symptom Distress Index (PSDI) T Score, Global Severity Index (GSI) T Score and Positive Symptom Total (PST) Difference (with 95% Confidence Interval, CI) per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3) In Normative Aging Study, 2000-2014. (Multi-pollutant Model, Including People on Psychiatric Medication)

		Psychiatric Medication Use Adjusted		
Exposure	**Window**	**Estimate [a] (95% CI)**	**Estimate [a] (95% CI)**	**Estimate [a] (95% CI)**
		PSDI T Score [b]	**GSI T Score [b]**	**PST [b]**
NO_2	1Wk	1.14 (0.00, 2.28)	0.12 (-0.90, 1.15)	-0.20 (-1.12, 0.73)
	4Wk	1.51 (0.13, 2.89)	0.16 (-1.08, 1.41)	-0.22 (-1.36, 0.91)
	8Wk	1.24 (-0.21, 2.69)	-0.06 (-1.36, 1.23)	-0.43 (-1.62, 0.75)
	1Yr	1.05 (-0.45, 2.55)	-0.77 (-2.10, 0.57)	-0.77 (-1.99, 0.45)
O_3	1Wk	1.73 (0.82, 2.64)	0.36 (-0.49, 1.20)	-0.08 (-0.83, 0.68)
	4Wk	1.31 (0.27, 2.35)	-0.07 (-1.05, 0.90)	-0.42 (-1.29, 0.44)
	8Wk	0.91 (-0.19, 2.01)	-0.20 (-1.22, 0.83)	-0.41 (-1.32, 0.50)
	1Yr	1.33 (0.11, 2.55)	0.24 (-0.87, 1.34)	-0.26 (-1.25, 0.73)
$PM_{2.5}$	1Wk	-0.53 (-1.21, 0.16)	-0.23 (-0.88, 0.41)	-0.28 (-0.85, 0.30)
	4Wk	-0.12 (-1.00, 0.77)	0.09 (-0.72, 0.90)	-0.02 (-0.75, 0.71)
	8Wk	0.22 (-0.69, 1.13)	0.21 (-0.60, 1.02)	0.06 (-0.66, 0.79)
	1Yr	-1.26 (-2.82, 0.31)	-0.02 (-1.47, 1.43)	-0.13 (-1.44, 1.19)

Annotation: [a] Difference in the global scores per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3); [b] Adjusted for co-exposures, temperature (except for 1 Yr window), relative humidity, calendar year, age, bmi, race, education, marital status, season, census tract median household income, census tract median value of house, census tract population density and psychiatric medication use (yes or no). 1Wk, 4Wk, 8Wk and 1Yr means for the exposure windows of average 1 week, 4 weeks, 8 weeks and one year prior to the visit date. Psychiatric medication use includes the use of antidepressants and anti-anxiety drugs.

eTable 4. Brief Symptom Inventory Positive Symptom Distress Index (PSDI) T Score, Global Severity Index (GSI) T Score and Positive Symptom Total (PST) Difference (with 95% Confidence Interval, CI) per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3) Over 1 Year Prior To Visit Window In Normative Aging Study, 2000-2014. (Multi-pollutant Model Adjusting for Average Temperature 1 Yr Prior to Visit)

Exposure	Estimate [a] (95% CI) Model I [b]	Estimate (95% CI) Model II [c]	Outcome
NO_2	1.37 (-0.29, 3.03)	1.06 (-0.65, 2.77)	PSDI T
O_3	1.04 (-0.31, 2.39)	1.06 (-0.31, 2.43)	
$PM_{2.5}$	-0.98 (-2.72, 0.75)	-0.90 (-2.71, 0.91)	
NO_2	-0.45 (-1.91, 1.01)	-0.53 (-2.04, 0.97)	GSI T
O_3	0.34 (-0.83, 1.52)	0.40 (-0.81, 1.62)	
$PM_{2.5}$	-0.10 (-1.68, 1.47)	-0.11 (-1.75, 1.54)	
NO_2	-0.20 (-1.52, 1.13)	-0.26 (-1.61, 1.08)	PST
O_3	-0.12 (-1.17, 0.93)	0.02 (-1.04, 1.09)	
$PM_{2.5}$	-0.27 (-1.67, 1.14)	-0.29 (-1.75, 1.17)	

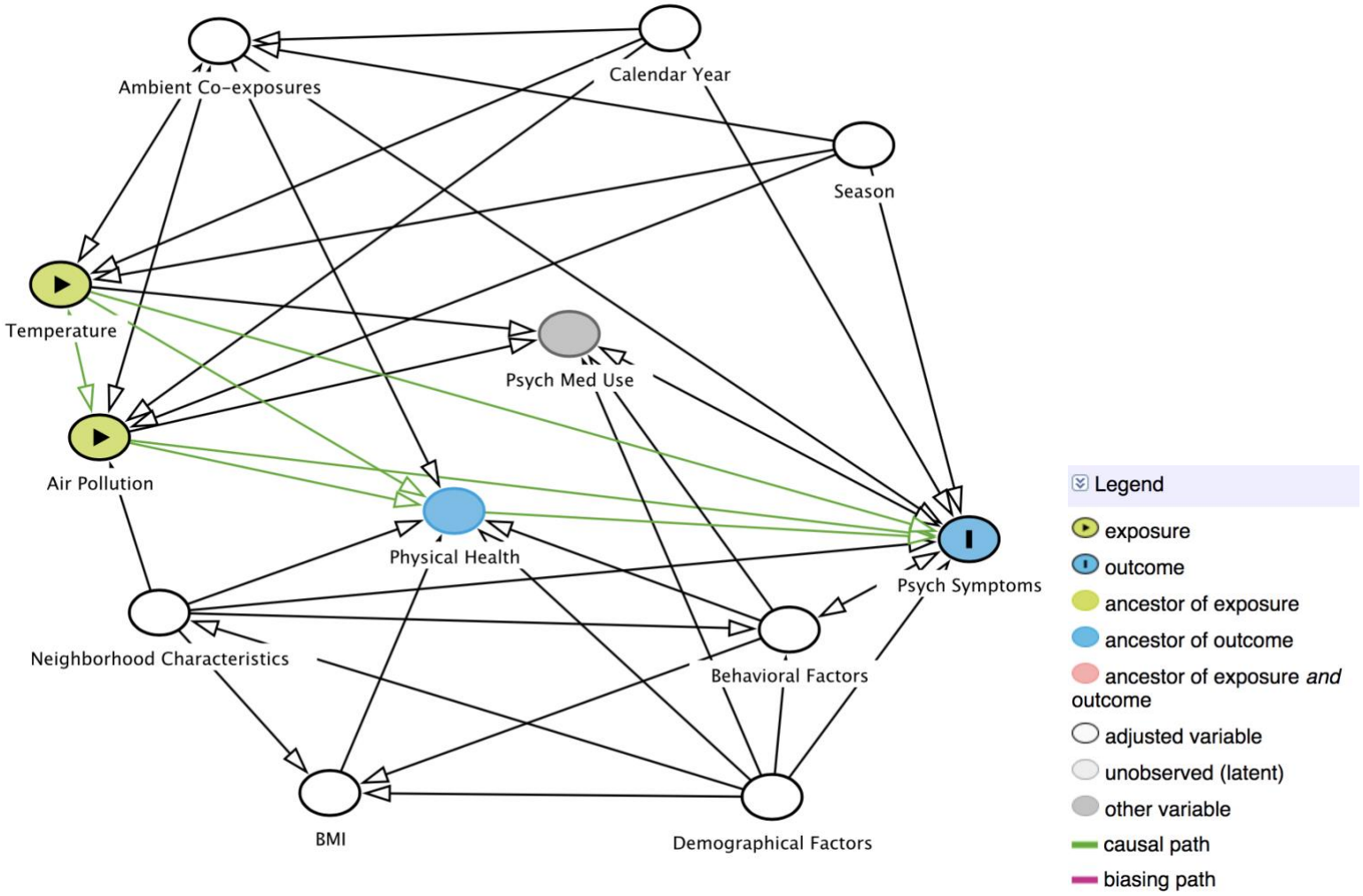
Annotation: [a] Difference in the global scores per Interquartile Increase of Exposures of Interest (NO_2 – ppb, O_3 – ppb, $PM_{2.5}$ - μg/m^3) over the 1 Yr prior to visit exposure window; [b] Adjusted for co-exposures, temperature, relative humidity, calendar year, age, bmi, race, education, marital status, season, census tract median household income, census tract median value of house, census tract population density; [c] Adjusted for the covariates adjusted in Model I plus physical activity (using total metabolic equivalent of task (hours/week)), smoking and drinking.

eTable 5. Associations Between Being Selected into The Study and Increased Exposure to Each Air Pollutant

Exposures (average 4 weeks before as an example)	**OR (95% CI)** [a] on the chance of being selected
$PM_{2.5}$	0.97 (0.91, 1.03)
O_3	1.01 (0.99, 1.03)
NO_2	0.98 (0.96, 1.00)

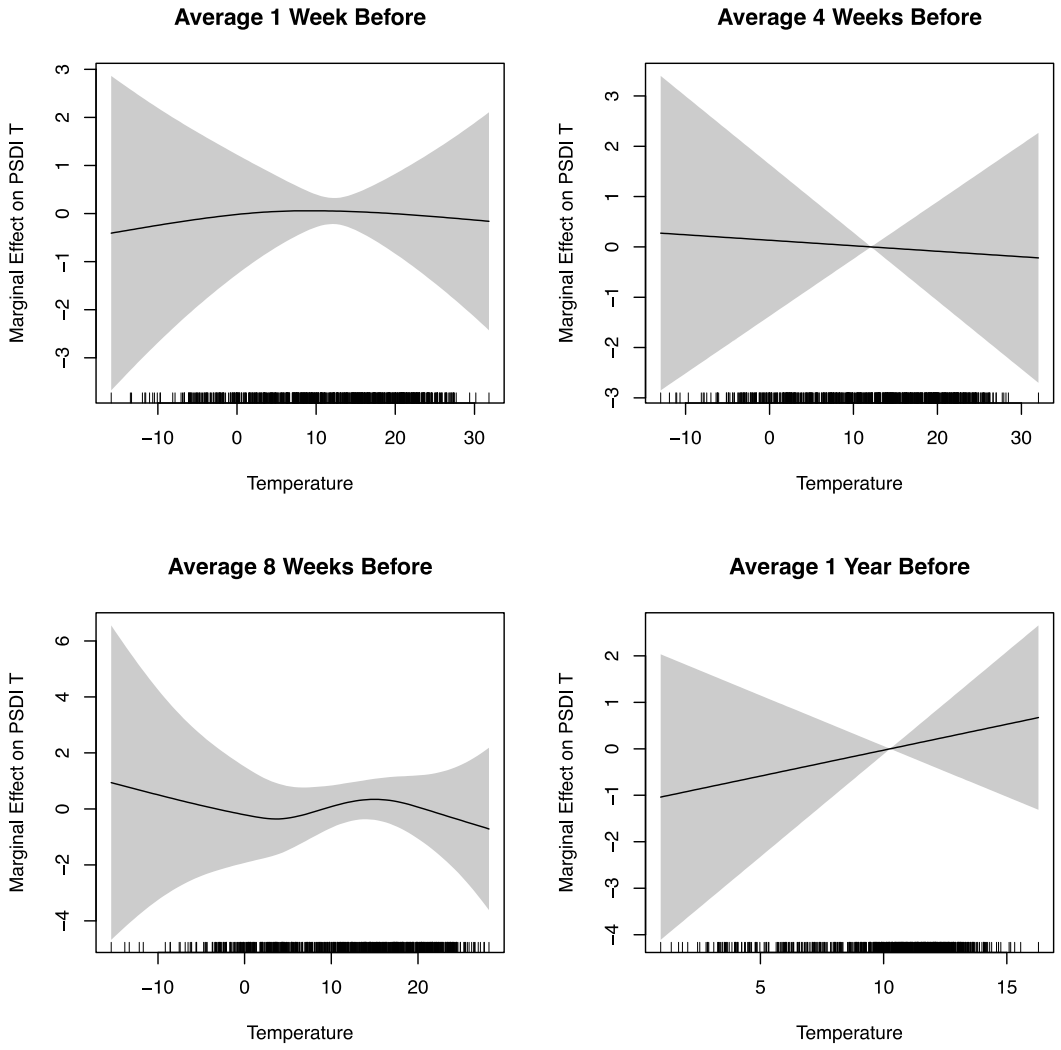
Annotation: [a] Odds ratio and 95% confidence intervals (CI) of being selected per 1 unit Increase of Exposures of Interest ($PM_{2.5}$ - $\mu g/m^3$, O_3 - ppb, NO_2 - ppb)

eFigure 1. Proposed Directed Acyclic Graph (DAG) on Studying Epidemiological Confounding Structure of Air Pollution and Psychiatric Symptom in Normative Aging Study

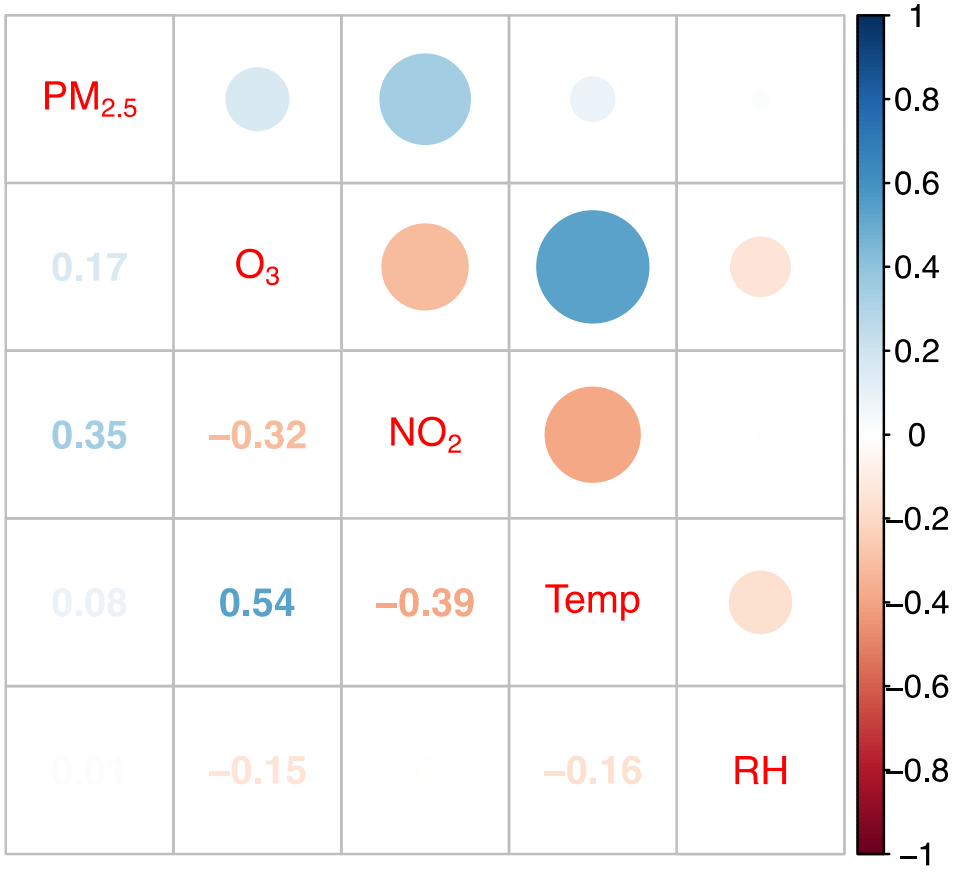


Annotation: The plot showed the directed acyclic graph on studying the associations between air pollution and psychiatric symptoms measured in the Normative Aging Study. **Ambient Co-exposures** include the other air pollutants and meteorological variables (i.e. co-exposures and relative humidity) besides the one of focus reported each time in the analysis ($PM_{2.5,}$ ozone or NO_2); **Psych Symptoms** is psychiatric symptoms; **Psych Med Use** is the psychiatric related medication use; **Physical Health** includes a list of physical health measurements such as total cholesterol, HDL cholesterol, serum triglyceride, fasting glucose, coronary heart disease, stroke, percent predicted FEV and hypertension at the visit; **Neighborhood Characteristics** include census tract level median household income, median value of house and population density; **BMI** is the body mass index (kg/m^2); **Demographical Factors** adjusted in this study include age, race, education and marital status; **Behavioral Factors** adjusted in this study include smoking, drinking and physical activity level as measured by total metabolic equivalent of task (hours/week).

eFigure 2. Temperature - Response Curves Over Average 1 Week, 4 Weeks, 8 Weeks and 1 Year Windows Prior to Visit - Using Positive Symptom Distress Index (PSDI) T Score as Example, Model I Adjustment)



eFigure 3. Correlation of Ambient Exposures for Average 1 Week Window Prior to Visit



Annotation: The plot showed the spearman correlation coefficient for each pair of ambient exposures including fine particulate matter ($PM_{2.5}$), ozone (O_3), nitrogen dioxide (NO_2), temperature (Temp) and relative humidity (RH) at average 1 week prior to visit date. Blue circles/numbers represent negative correlation coefficients while red ones indicate positive correlation coefficients. The darker the color is, the higher the corresponding correlation coefficient is.

References:

Scott D, Happell B. 2011. The high prevalence of poor physical health and unhealthy lifestyle behaviours in individuals with severe mental illness. Issues in mental health nursing 32:589-597.
Sheppard L, Burnett RT, Szpiro AA, Kim S-Y, Jerrett M, Pope CA, et al. 2012. Confounding and exposure measurement error in air pollution epidemiology. Air Quality, Atmosphere & Health 5:203-216.