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DIABETES

ABSTRACT & COMMENTARY

Fruits and Vegetables Lower the Risk of Type 2 Diabetes

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Dr. Hood and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: A multicenter, multinational prospective case-cohort study concludes that an increase in dietary consumption of fruits and vegetables is beneficial in reducing the risk of diabetes mellitus type 2 regardless of the current level of consumption.

SOURCE: Zheng JS, Sharp SJ, Imamura F, et al. Association of plasma biomarkers of fruit and vegetable intake with incident type 2 diabetes: EPIC-InterAct case-cohort study in eight European countries. *BMJ 2020*;370:m2194.

The estimated risk of developing diabetes continues to increase throughout the world. The average risk of developing type 2 diabetes (T2D) for persons born in the United States in 2000 is 32.8% for males and 38.5% for females. The estimated risk for Hispanic persons born in the United States is 45.4% for men and 52.5% for women, the highest in the country.[1] Any effective strategy for risk reduction and prevention has significant public health implications. Citing inconsistent, weak evidence from prospective studies and sparse randomized control trials linking fruit and vegetable intake with T2D risk reduction, Zheng et al aimed to examine the association of baseline levels of circulating vitamin C and carotenoids with incident T2D. The investigators used data collected in the European Prospective Investigation into Cancer and Nutrition (EPIC), an ongoing, multi-center prospective cohort study designed to investigate the links between nutrition and cancer risk in more than 500,000 community-based adult subjects from eight European countries.[2]

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Summary Points

- Measurements of plasma vitamin C and carotenoids serve as reliable objective surrogates for self-reported consumption of fruits and vegetables.
- There is an inverse association between vitamin C and carotenoid levels and the development of incident type 2 diabetes (T2D).
- Increasing daily servings of fruits and vegetables reduces the risk of T2D regardless of baseline consumption.
- Vitamin supplements alone do not reduce risk.

According to the case-cohort study design, and after exclusions for missing or inadequate blood samples, the authors included data from a population of 22,833 subjects from the EPIC-InterAct subcohort (total > 340,000 participants) nested within the EPIC study. The population consisted of 9,754 participants with incident T2D and 13,662 randomly selected sub-cohort participants with an average follow-up of 9.7 years across 26 study centers in eight European countries. Nonfasting blood samples, collected from subjects at the EPIC study's baseline visit, were used to obtain plasma levels of vitamin C, and several carotenoids (alpha-carotene, beta-carotene, lycopene, lutein, zeaxanthin, and beta-cryptoxanthin) were measured via the high-performance liquid chromatography-ultraviolet method.

Additional baseline data included weight, height, and waist circumference. Baseline physical activity, smoking status, sociodemographic factors, and medical history were obtained by study staff from self-administered questionnaires. The self-reported diabetic status of subjects was ascertained by primary and secondary care registers, drug registers, and hospital and mortality records.

Using averages of the standardized values of vitamin C and individual carotenoid levels in the subcohort, a composite biomarker score was calculated and applied to analyses, along with analyses of the effect of individual biomarker levels. The composite biomarker score was correlated with subject self-report of fruit and vegetable intake; differences in total intake were determined for each one standard deviation increase in composite biomarker score using linear regression. Adjustments in all analyses were made for confounding factors, including age, sex, sociodemographic factors (marital status and education), physical activity, smoking, body mass index (BMI), energy intake, alcohol, waist circumference, and diet (cereals, potatoes, soft drinks, legumes, nuts, eggs, fish, red meat, and vitamin supplementation).

Composite biomarker scores were divided into five categories, correlating with lowest consumption of fruits and vegetables (Group 1) to highest consumption (Group 5). These categories then were correlated with incident T2D, continuing to adjust for other confounding risk factors, including obesity, family history of T2D, insulin resistance, cardiovascular disease, cancer, stroke, menopausal status, and diet quality. Additionally, in order to investigate the association between incident T2D and current "five a day" recommendations for fruit and vegetable serving consumption, the authors used composite biomarker levels to identify subjects in two groups: those meeting or exceeding five servings a day (> 400 g) and those not meeting current recommendations.

Results, summarized in Table 1, focused on incident T2D and composite biomarker scores from Groups 2, 3, 4, and 5 compared to Group 1. They were applied in a primary reference statistical model, 1a, adjusting for age, sex, and research center. Two additional models adjusted for confounding risk factors: model 1b, further adjusting for physical activity, smoking, alcohol, total energy intake, sociodemographic factors, high-density lipoprotein and low-density lipoprotein levels; and model 2, additionally adjusting for BMI and adiposity. Although adjustments in these models attenuated the magnitude of the inverse association trends, all remained statistically significant ($P < 0.001$).

Subjects with incident T2D had lower mean concentrations of plasma vitamin C and total carotenoids compared to the subcohort population. There was an inverse association

Table 1. Associations Between Composite Biomarker Scores and Incident Type 2 Diabetes

	Hazard Ratio (95% Confidence Interval)						
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**For Each SD**	***P* Value**
Median daily fruit and vegetable intake (g)	274	357	396	452	508		
Median composite biomarker score	-0.66	-0.31	-0.05	0.23	0.74		
Type 2 diabetes cases/ person years	2,752/10,909	1,719/13,249	1,249/14,624	1,047/15,582	770/17,471		
Model 1a	1.0 (reference)	0.61 (0.53-0.70)	0.43 (0.35-0.53)	0.32 (0.24-0.43)	0.22 (0.17-0.30)	0.55 (0.48-0.63)	< 0.001
Model 1b	1.0 (reference)	0.67 (0.59-0.77)	0.52 (0.44-0.62)	0.42 (0.33-0.52)	0.31 (0.25-0.39)	0.61 (0.55-0.69)	< 0.001
Model 2	1.0 (reference)	0.77 (0.68-0.87)	0.66 (0.54-0.80)	0.50 (0.40-0.62)	0.50 (0.40-0.62)	0.75 (0.67-0.83)	< 0.001

SD: standard deviation; model 1a: age, sex, and research center; model 1b: 1a plus physical activity, smoking, employment, marital status, education, alcohol intake, total energy intake, and high-density lipoprotein and low-density lipoprotein levels; model 2: 1b plus adiposity (body mass index and waist circumference)

between incident T2D and composite biomarker scores, as well as total vitamin C and total carotenoids.

Additionally, an inverse association with incident T2D was noted for all individual plasma carotenoids, except for zeaxanthin. The hazard ratios comparing Groups 2, 3, 4, and 5 of the composite biomarker score with Group 1 were 0.77 (95% confidence interval [CI], 0.68-0.87), 0.66 (95% CI, 0.54-0.80), 0.59 (95% CI, 0.48-0.72), and 0.50 (95% CI, 0.40-0.62), respectively, for model 2, which included adjustments for all confounding risk factors. Analysis comparing "five or more servings per day" to fewer than five servings daily and incident T2D resulted in a hazard ratio of 0.69 (95% CI, 0.63-0.76). A single standard deviation difference in the composite biomarker score, equivalent to approximately 66 g difference in daily fruit and vegetable intake, was associated with a hazard ratio of 0.75 (95% CI, 0.67-0.83; $P < 0.001$).

■ COMMENTARY

The strengths of this study include its case-cohort design, the large number of subjects with complete data sets from the EPIC database, the use of quantitative measures of fruit and vegetable consumption biomarkers that correlated well with subject self-report of daily intake, and the care the researchers took to statistically adjust dietary association results for other confounding risk factors for incident T2D. This study supports the current nutrition recommendation by several national and international organizations (American Heart Association, United States Department of Agriculture, Centers for Disease Control and Prevention, World Health Organization, et al) to consume five total servings of fruits and vegetables daily. It also provides evidence for encouraging patients with low intake to add daily servings toward meeting these recommendations, with each increase of about 66 g in daily consumption of fruits and vegetables appearing to significantly reduce the risk of developing T2D.

For patients who adhere to this recommendation, evidence exists for further risk reduction when consumption exceeds the five recommended servings per day. Further, as noted in previous studies, vitamin supplements do not have the same associations with risk reduction as whole fruits and vegetables. Thus, it is unlikely that these vitamins identified as biomarkers for fruits and vegetables are solely bio-physiologically responsible for risk-mitigating effects.

How can clinicians use this information? Patients can be confidently encouraged to increase their intake of fruits and vegetables and assured that even small increments make a difference. The 66-g increment associated with a standard deviation in biomarker plasma level amounts to about half of a medium apple, one medium raw carrot, one cup of chopped broccoli, or one cup of chopped kale. When patients ask if they can just take a vitamin supplement, we can cite this study as ongoing evidence that the value of whole food is much more than the vitamins contained therein. The common wisdom reflected in author Michael Pollan's aphorism, now more than a decade old, rings loud and clear in these study results: "Eat food, not too much, mostly plants."[3] ■

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ABSTRACT & COMMENTARY

Childhood Sleep Difficulties and Adolescent Mental Health

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: This prospective United Kingdom study involving 13,488 children shows an association between specific early childhood sleep problems and symptoms of psychosis in adolescence. Another specified early childhood sleep problem is associated with symptoms of borderline personality disorder in adolescence.

SOURCE: Morales-Muñoz I, Broome MR, Marwaha S. Association of parent-reported sleep problems in early childhood with psychotic and borderline personality disorder symptoms in adolescence. *JAMA Psychiatry* 2020:e201875 [Epub ahead of print].

The last 10 years have shown an upsurge in research efforts aimed at understanding the etiology of mental health problems. The search for early onset, modifiable risk factors for behavioral and emotional disorders has received particular attention. Studies point toward poor sleep in early childhood as having relevance for the development of later psychopathology.[1,2]

Several studies have linked early childhood nightmares to psychotic experiences in teenage years, and one study has suggested a similar association between childhood nightmares and borderline personality disorder (BPD) symptoms in pre-adolescence. The relationship remains unclear, and some researchers suspect that poor childhood sleep could be a precursor to depression and, thus, put an child at risk for other mental health disorders.[2,3]

BPD typically is considered a disorder presenting in adult years. However, there is growing evidence of BPD symptoms in up to 3% of children as young as 11 years of age. Diagnostic criteria are identical to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for BPD in adults — with the caveat that there is at least one year of "immature personality development" with disruption in at least five of the following areas:

- Unstable interpersonal relationships
- Identity disturbance
- Impulsivity
- Suicidal and/or self-harming behaviors
- Mood instability
- Feelings of emptiness
- Inappropriate and intense anger
- Paranoias under stressful circumstances[4]

Individuals with BPD often present with psychotic experiences, such as hallucinations or delusions. However, psychosis in adolescence may occur in association with other disorders of mental health, including depression, anxiety, trauma response, substance abuse, as well as schizophrenia.[5] Although BPD symptoms are believed to occur in about 3% of adolescents and psychotic symptoms in 7.5% of adolescents, behavioral sleep problems in young children are significantly more common, occurring in 15% to 30% of children under the age of 5 years.[6] Thus, it becomes important to clarify what type of sleep problems are higher risk or more likely to be associated with the development of symptoms of mental health problems as children reach their teenage years.

To add to the growing knowledge about this relationship, Morales-Muñoz et al used a data base of participants in the Avon Longitudinal Study of Parents and Children (ALSPAC), a United Kingdom study in the early 1990s that recruited pregnant women and followed their children from birth through the stages of development. From this cohort group, the team was able to obtain data from 7,155 children reporting on psychotic experiences between the ages of 12 and 13 years and 6,333 children evaluated for symptoms of BPD between the ages of 11 and 12 years. These children responded to a questionnaire at age 10 years regarding depressive symptoms.

Psychotic symptoms were evaluated via the Psychosis-Like Symptom Interview (PLSI),[7] and BPD symptoms were assessed using the United Kingdom Childhood Interview for DSM-4 Borderline Personality Disorder.[4] The Total Mood and Feelings questionnaire (13 items) was used to evaluate degree or presence of depression.[8] The behavioral sleep disorders included night sleep duration, bedtime, night awakenings, and regular sleep routine. These were recorded at ages 6 months, 18 months, 30 months, 3.5 years, 4.8 years, and 5.8 years. When adjusted for variables, such as family adversity, child abuse, sex of the child, maternal age, and prematurity, several significant findings emerged. Results were divided into two sections: the first regarding psychotic symptoms at

Summary Points

- The Avon Longitudinal Study of Parents and Children (ALSPAC) recruited pregnant woman in the early 1990s and followed their children from birth onward.
- Children were seen at specific ages, and parents were asked each time about children's sleep habits.
- Depression was assessed at age 10 years via questionnaire; in-person interviews were conducted at 11-12 years of age to determine if symptoms of borderline personality disorder (BPD) were present and between 12-13 years of age to evaluate for psychotic experiences.
- Frequent night awakenings at 18 months and irregular sleep patterns at 6 months, 30 months, and 5.8 years were significantly linked to psychotic experiences by the age of 12-13 years; the significance of frequent night awakenings at 18 months and an irregular sleep routine at 5.8 years appeared to be mediated by depression at 10 years of age.
- Shorter nighttime sleep at age 3.5 years was significantly linked to BPD symptoms by age 11-12 years.

ages 12 to 13 years and the second regarding BPD symptoms at age 11 to 12 years.

Association of behavioral sleep problems of childhood and psychotic symptoms ages 12-13 years as measured by PLSI:

- Frequent night awakenings at age 18 months was associated with psychotic symptoms at age 12-13 years with odds ratio (OR) 1.13 (95% confidence interval [CI], 1.01-1.26); $P = 0.03$.
- Irregular sleep routine at ages 6 months, 30 months, and 5.8 years was associated with psychotic symptoms at age 12-13 years.
  - 6 months: OR 0.68 (95%CI, 0.50-0.93); $P = 0.02$
  - 30 months: OR 0.64 (95%CI, 0.44-0.95); $P = 0.02$

Association of behavioral sleep problems of childhood and BPD symptoms at age 11-12 years as measured by the United Kingdom Childhood Interview for DSM-4 Borderline Personality Disorder.

- Shorter nighttime sleep duration at age 3.5 years was associated with BPD symptoms by age 11-12 years, with OR 0.78 (95% CI, 0.66-0.92); $P = 0.004$.
- When adjusted for depression, there appeared to be no mediating effect on this relationship.

■ COMMENTARY

In many ways, this Morales-Muñoz et al investigation gives rise to more questions than answers. The results indicate an association between adolescent psychotic symptoms and higher frequency of night awakenings at age 18 months and/or irregular sleep routines at ages 6 months, 30 months, and 5.8 years. Depression at age 10 mediated some of these findings (frequent night awakening at age 18 months and irregular sleep routine at age 5.8 years.) Additionally, BPD symptoms in pre-adolescents were associated with shorter nighttime sleep duration at age 3.5 years. This result was not mediated by depression at age 10 years. These findings clearly point to a role of sleep in psychopathology and suggest that sleep problems may predate mental health symptoms. The disparate results may reflect separate pathways of development for psychosis and BPD.

Perhaps the largest question raised by these findings is in the area of prevention. Although the hope is that modifying sleep patterns early in life can affect later psychopathology, this study simply cannot provide evidence of such a relationship. It may be that the disrupted sleep patterns reflect an early-onset symptom, rather than a cause of a later-emerging mental health disorder. Additionally, it is important to consider that poor sleep in a child can be extremely disruptive to family life, and, likewise, a disruptive family life can trigger poor sleep habits. The question of the "chicken or the egg" most likely has relevance here; clarification via further studies can help delineate treatment pathways. Even considering the limitations, the findings do raise the possibility of correcting sleep disruption early in life to help prevent or mitigate later psychopathology. This is an area of clinical importance, especially in families with a genetic risk of mental health disorders. A primary care physician is well-positioned to discuss sleep hygiene and sleep regulation with families and remind parents of the importance of establishing bedtime routines while children are young. It is worth keeping in mind that children with constitutionally poor sleep may be at higher risk of developing mental health disorders, and individualizing a plan for these children and families may be the best way to proceed. ■

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COGNITION

ABSTRACT & COMMENTARY

Air Pollution and Cognitive Decline

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Dr. Nomigolzar and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: In this large prospective cohort study of subjects in Manhattan, researchers demonstrated an association between exposure to air pollution and decline in cognitive function over time in one cohort, but not the other.

SOURCE: Kulick ER, Wellenius GA, Boehme AK, et al. Long-term exposure to air pollution and trajectories of cognitive decline among older adults. *Neurology* 2020;94:e1782-1792.

Air pollutants are potent oxidants that can lead to oxidative stress and inflammation.[1] As a result, ambient air pollution has been associated with various cardiovascular and respiratory diseases.[2-3] Recently, there has been a growing interest in a potential link between air pollution and neurological damage, especially in the elderly, for whom cognitive decline is a major mobidity.[4] Despite evidence of a pathological central nervous system vascular inflammatory effect of air pollution from animal experiments and human autopsy studies, cohort study results relating longitudinal exposure to air pollution and cognitive decline have been mixed.[5-9]

In the study reviewed, Kulick et al used data from two prospective cohorts of individuals residing in the northern Manhattan area of New York City to investigate the association between long-term exposure to ambient air pollution and cognitive decline, both cross-sectionally and longitudinally. The data collection was obtained from two ongoing prospective cohort studies of residents in northern Manhattan: the Washington Heights-Inwood Community Aging Project (WHICAP) and the Northern Manhattan Study (NOMAS). WHICAP is a study of aging and dementia and recruited its participants in three different waves in 1992, 1999, and 2010. WHICAP used the following inclusion criteria:

- equal proportion of Hispanic, non-Hispanic Black, and non-Hispanic White participants;
- equal proportion of participants age 65-74 years and > 75 years.

Subjects with substantial cognitive problems, history of dementia, or who were unable to speak English or Spanish were excluded. Additional participants were selected from the NOMAS project, established to study stroke risk factors prospectively in multiethnic individuals living in the same community. Participants were recruited between 1993 and 2001 and 2003 and 2008. A subcohort of NOMAS recruits received neuropsychological assessment as a baseline between 2003 and 2008. Inclusion criteria for this group were:

- age > 50 years;
- no clinical stroke or clinically identified dementia;
- no contraindications to magnetic resonance imaging.

All individuals from this cohort had at least one follow-up neuropsychological assessment after five years. The final sample selected by Kulick et al for data analysis (n = 5,330 from WHICAP; n = 1,093 from NOMAS) included those subjects with no baseline dementia, at least one neuropsychological exam during the study, whose primary address was in New York City, and no missing data for the confounding variables.

Satellite and Environmental Protection Agency data for nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and respirable particulate matter (PM_{10}) were used in validated, regionalized, universal geostatistical kriging models to estimate the residential air pollution exposure in the calendar year prior to enrollment. Cognitive function, represented by a global cognitive score, was

Summary Points

- Despite evidence of a pathological central nervous system vascular inflammatory effect of air pollution from animal experiments and human autopsy studies, cohort study results relating longitudinal exposure to air pollution and cognitive decline have been mixed.
- In this analysis of data from two large prospective study cohorts living in the same limited geographical area in northern Manhattan, researchers investigated the relationship between exposure to air pollution and evidence of cognitive decline. They based their findings on global cognition scores measured by periodic administration of validated neuropsychological testing.
- Evidence of cognitive decline was associated with higher levels of ambient air pollution in both cross-sectional and longitudinal analyses for one large cohort, but not the other.

calculated using validated neuropsychological tests assessing three domains of cognitive function (memory, executive function, language) and standardized as *Z*-scores with cohort-specific means and standard deviations. Sociodemographic data for analysis included age at time of cognitive testing, race-ethnicity, and educational level. A summary *Z*-score for socioeconomic status was calculated for each subject based on census information of neighborhood measures of wealth, education and occupation. Data from the WHICAP and NOMAS cohorts were analyzed separately. Linear mixed models were used for repeated measures assessing the relationship between exposure to air pollutants and both baseline cognitive function and cognitive decline. Data analysis suggests that in the WHICAP cohort, higher levels of ambient air pollution were associated with cognitive decline at baseline as well as a higher rate of cognitive decline over time. (*See Table 1.*) However, in NOMAS, there was no significant association between residential ambient air pollution and baseline cognitive decline or rate of decline in cognitive function.

■ COMMENTARY

The populations in WHICAP and NOMAS were similar in most aspects except that NOMAS had a younger cohort, with a median age of 70 years (±9.0) compared to WHICAP's 75.2 years (±6.46), lower prevalence of cardiovascular disease, and included a higher percentage of Hispanic individuals (43% in WHICAP, 66% in NOMAS). The mean levels of air pollutants also were similar between the two groups, but NOMAS had less variability in pollutant levels. These differences between WHICAP and NOMAS were cited by the authors as possible explanations for the differences in observed outcomes between the two cohorts. The younger NOMAS cohort could explain the better baseline cognition as well as less decline in cognition upon follow-up for this group. Moreover, individuals in the WHICAP cohort had more cardiovascular diseases, which may have contributed to greater decline in cognition.

Interestingly, the greater percentage of Hispanic individuals in the NOMAS cohort suggests a potential underlying protective factor in Hispanic populations, possibly as the result of genetics or lifestyle factors, such as nutrition, exercise, and alcohol use. Another factor that might have influenced outcomes is that WHICAP was a significantly larger cohort, which increases the power of the data analysis compared to NOMAS. Finally, the NOMAS data excluded individuals with pre-existing dementia and history of stroke or cardiac events, creating a potential selection bias.

Table 1. Associations Between Ambient Air Pollution and Global Cognitive Score

		Difference in Cognitive Scores* (95% CI)		
		NO_2	$PM_{2.5}$	PM_{10}
WHICAP Global Cognitive Score	Baseline cognition	-0.218 (-0.299 to -0.136)	-0.109 (-0.197 to -0.021)	-0.056 (-0.108 to -0.004)
	Cognitive decline	-0.062 (-0.082 to -0.041)	-0.066 (-0.085 to -0.048)	-0.030 (-0.046 to -0.014)
NOMAS Global Cognitive Score	Baseline cognition	0.032 (-0.020 to 0.083)	0.045 (-0.026 to 0.116)	0.001 (-0.056 to 0.058)
	Cognitive decline	-0.004 (-0.040 to 0.032)	-0.015 (-0.065 to 0.034)	-0.019 (-0.059 to 0.022)

CI = confidence interval; NO_2 = nitrogen dioxide; $PM_{2.5}$ = fine particulate matter fewer than 2.5 micrometers in diameter; PM_{10} = respirable particulate matter.
* β indicates standard deviation change in cognitive score associated with an interquartile range change in pollutant. Cognitive decline defined in model as β estimate of pollutant x visit.

Even though this study had some limitations, and findings were not consistent between the two cohorts, the results of WHICAP adds to the evidence base linking higher levels of ambient air pollution with accelerated cognitive decline. Further studies on this topic will help to solidify the association between ambient air pollution and cognitive decline. In the meantime, the findings can help physicians become more sensitive to the possibility of accelerated cognitive decline in their patients and maintain increased vigilance for early symptoms and signs. Although many patients may not be able to move away from high pollution, awareness of this modifiable risk factor can help physicians focus on preventive measures, such as increasing indoor air quality with air purifiers and patient education concerning home cleaning and regular air filter changes. Finally, physicians who are so inclined may use this data to support ongoing public and political advocacy for clean air. ■

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CME QUESTIONS

1. **Which of the following best describes the association between daily fruit and vegetable intake and incident type 2 diabetes in the case-cohort study reported by Zheng et al?**
   a. Vitamin C and carotenoid biomarkers correlated poorly with subjects' self-reported intake.
   b. A 66-g-per-day increase in total daily intake was associated with statistically significant risk reduction.
   c. Individual vitamin C and carotenoid levels were not associated with significant risk reduction.
   d. Adjustments of risk calculation for other known risk factors negated all inverse risk associations.

2. **According to the study regarding sleep in childhood and adolescent mental health problems:**
   a. behavioral sleep problems occur in fewer than 10% of young children; children with any such problems are at high risk for depression, psychosis, or symptoms of borderline personality disorder (BPD) by preteen to teen years of age.
   b. behavioral sleep problems occur in up to 30% of young children; addressing the majority of such problems is likely to prevent the development of specific mental health disorders.
   c. behavioral sleep problems occur in up to 30% of young children; there is an association of specific sleep problems with symptoms of BPD or psychosis at adolescence, although a portion of the association with psychotic symptoms is mediated by depressive symptoms by 10 years of age.
   d. behavioral sleep problems occur in fewer than 10% of young children; there is an association of specific sleep problems with development of symptoms of BPD or psychosis by teenage years, but this association is almost entirely mediated by depressive symptoms by 10 years of age.

3. **In the study by Kulick et al, which of the following reasons was suggested for the lack of association between higher levels of air pollution and cognitive decline in the Northern Manhattan Study cohort?**
   a. The subjects were from a different urban area.
   b. The cohort's mean age was younger.
   c. The mean ambient air pollutant levels were lower.
   d. The cohort included fewer Hispanic subjects.

[IN FUTURE ISSUES]

Mindfulness at an FQHC

Air Filters Shown to Improve Breathing in Children With Asthma

Volunteering and Health and Well-Being in Older Adults