

## News and Views

### Subclinical Small Airway Dysfunction in Young Smokers

Young smokers, aged 30 to 45 years, have already established changes in their small airways, lung parenchyma and pulmonary vasculature evident on CT scan, suggestive of subclinical small airway dysfunction, independent of the severity of symptoms. These abnormalities are associated with a faster decline in lung function. These findings from a study in the United Kingdom was published May 15, 2024 in the *American Journal of Respiratory and Critical Care Medicine*<sup>1</sup>.

The researchers gathered data on symptoms using the COPD Assessment Test (CAT), spirometry, and lung structure via quantitative thoracic computed tomography (QCT) scans from 431 current smokers, median age 39 years and 16 pack-years smoking history. They were recruited from the BEACON (British Early COPD Network) cohort with normal spirometry findings. Sixty-seven nonsmokers were selected as controls. Three hundred fifty-eight subjects were assessed every 6 months, over a median follow-up duration of 32 months, with postbronchodilator spirometry to track the rate of decline in forced expiratory volume in 1 second (FEV<sub>1</sub>). The objectives were to determine if structural changes in the lungs can be detected early in the course of the disease and also how these structural changes correlated with the rate of FEV<sub>1</sub> decline over time.

The young smokers and never-smoking controls did not differ significantly in terms of demographic characteristics or subjective CT appearances. However, 24.2% of the young smokers were found to have chronic bronchitis, and 55.7% had CAT scores higher than 10 indicating significant respiratory symptoms.

In comparison to control subjects, findings on QCT scan indicative of high disease probability were increased in smokers. Functional small airway disease, ground-glass opacification, bronchovascular prominence and the ratio of small blood vessel volume to total pulmonary vessel volume were elevated in smokers compared to controls. These QCT findings were all linked to a faster decline in FEV<sub>1</sub>. Higher CAT scores were also associated with a faster FEV<sub>1</sub> decline.

This study demonstrates that structural abnormalities associated with COPD detectable via CT scans in young smokers can serve as early indicators of COPD,

appearing before significant functional impairments or severe symptoms manifest. “Structural abnormalities are present early in the natural history of COPD and are markers of disease progression”, note the authors. These findings highlight the importance of early radiological screening in smokers to identify individuals at risk of developing COPD. Early detection provides an opportunity for more proactive monitoring and potential interventions to slow disease progression.

### Reference

1. Ritchie AI, et al; British Early COPD Network (BEACON) Cohort Investigators. Structural predictors of lung function decline in young smokers with normal spirometry. *Am J Respir Crit Care Med*. 2024;209(10):1208-18.

### Insulin Resistance and Diabetic Peripheral Neuropathy

Type 2 diabetes patients with low baseline estimated glucose disposal rate (EGDR) are at a significantly higher risk of developing diabetic peripheral neuropathy (DPN), according to the results of a 5-year follow-up study recently published in the *Journal of Diabetes*<sup>1</sup>.

A total of 366 type 2 diabetes patients without DPN were recruited from six localities in Shanghai between 2011 and 2014 for this prospective cohort study. They were followed up until 2019 or 2020. The Michigan Neuropathy Screening Instrument (MSNI) was used to assess neuropathy both at the time of enrollment and at the conclusion of the follow-up period. The objective of this study was to find out if eGDR could predict the risk of DPN.

Over the follow-up period of 5.91 years, 198 out of 366 individuals advanced to DPN based on the results of the MNSI examination with an overall incidence rate of 54.1%. Analysis of the impact of eGDR on the incidence of DPN revealed that participants with low baseline eGDR (eGDR <9.15) had greater incidence of DPN (62.3%) compared to those in the high baseline eGDR (eGDR ≥9.15) group (45.5%). This difference was statistically significant (p = 0.0013).

Subjects with sustained lower eGDR levels had a substantially higher incidence of DPN (63.6%) than individuals with sustained higher eGDR levels (35.8%). Even after controlling for other known risk factors for DPN, the elevated risk remained significant among

subjects with low baseline eGDR (eGDR <9.15) at the end of follow-up with odds ratio (OR) of 1.75.

eGDR is a novel biomarker for insulin sensitivity. The findings from this study demonstrates a strong link between eGDR levels and the incidence of DPN among patients with type 2 diabetes highlighting the role of insulin resistance in the development of neuropathy. Those with low eGDR levels appear to have a heightened susceptibility to DPN, as shown in this study, underscoring the importance of vigilant monitoring in these patients.

Early identification of patients with low eGDR is crucial as it allows timely interventions to prevent or delay the onset of neuropathy, a major risk factor for diabetic foot ulcers, which can substantially increase the probability of lower extremity amputations in diabetic patients. eGDR therefore may be incorporated into routine screening protocols for diabetic neuropathy. By monitoring eGDR, physicians can better manage and mitigate the neurological complications associated with diabetes, improving clinical outcomes and quality of life. They should be encouraged to adopt a healthy lifestyle with regular exercise and dietary modifications, to enhance insulin sensitivity to mitigate their risk of neuropathy.

#### Reference

1. Zhang Y, et al. Estimated glucose disposal rate predicts the risk of diabetic peripheral neuropathy in type 2 diabetes: A 5-year follow-up study. *J Diabetes*. 2024; 16(5):e13482.

### Too Much Exercise may Precede Hot Flashes in Menopausal Women

Acute changes in physical activity and ambient temperature may affect occurrence of hot flashes, according to a recent study from the United States published May 28, 2024 in the journal *Menopause*<sup>1</sup>.

In this study, a total of 270 women, aged 45 to 55 years, spanning three menopause stages, were equipped with ambulatory monitors to continuously measure temperature, humidity, physical activity and hot flashes over a 24-hour period. Data for the study was collected between October and April when the weather was cooler. Subjective hot flashes were documented via an event marker and data logging, while sternal skin conductance was used to objectively measure hot flashes. The participants wore accelerometers on the wrist to monitor physical activity and record the wake and sleep times. The study employed logistic multilevel modeling to examine the differences in physical activity,

humidity, and temperature in the 10 minutes before a hot flash compared to control windows where no hot flashes occurred. The odds of experiencing hot flashes were analyzed individually for objective hot flashes, subjective hot flashes, wake and sleep periods.

Data from 188 subjects was analyzed in the study. Acute increases in physical activity significantly increased the odds of objective waking hot flashes with OR of 1.31. Acute increases in physical activity also significantly increased the odds of subjective waking hot flashes (OR 1.16). The probabilities of experiencing an objective sleeping hot flash (OR 1.17) or a subjective sleeping hot flash (OR 1.72) were substantially higher when there were acute increases in the actigraphy signal.

Additionally, an increase in temperature was significantly associated with increased odds of experiencing subjective sleeping hot flashes (OR 1.38). Increased temperature was not associated with an increased risk of objective hot flashes. There was no evidence for a relationship between humidity and the chances of experiencing any hot flashes.

These findings suggest that overall hot flashes are more likely to occur when there is an acute increase in physical activity. Subjective hot flashes, but not objective hot flashes, are more likely to occur in higher ambient temperatures. While the beneficial effects of physical activity are well-known, clinicians should be aware of the association between physical activity and hot flashes and educate their patients about the link between too much exercise and hot flashes.

#### Reference

1. Witkowski S, et al. Acute increases in physical activity and temperature are associated with hot flash experience in midlife women. *Menopause*. 2024;31(7):600-7.

### Nutrient Profile for Healthy Brain Aging

A specific nutrient profile, which includes nutrients present in the Mediterranean diet, has been found to be associated with delayed brain aging, according to a study published in the journal *NPJ Aging*<sup>1</sup>.

Researchers at the University of Nebraska-Lincoln and University of Illinois in the United States collaborated for this multimodal cross-sectional study with 100 cognitively healthy participants aged 65 to 75 years. They were instructed to complete a questionnaire on demographic information, anthropometric measurements and physical activity. Fasting blood plasma samples were collected to measure 13 biomarkers of diet and nutrition. Cognitive evaluation was done with neuropsychological tests including the Wechsler Adult

Intelligence Scale (WAIS), the trail-making test from the Delis-Kaplan Executive Function System (DKEFS) and the Wechsler Memory Systems (WMS). They also underwent magnetic resonance imaging (MRI) scans to assess brain health.

In order to guide the formulation of dietary guidelines intended to support healthy brain aging, this study aimed to discover nutrient biomarker patterns that are linked with accelerated versus delayed brain aging. The brain phenotypes were categorized as measured by magnetic resonance spectroscopy (MRS). Performance on measures of intelligence, executive function, and memory were compared between the accelerated versus delayed brain aging phenotypes. The study also sought to determine dietary biomarker profiles, with an emphasis on elements from the Mediterranean diet that are known to benefit cognitive performance and brain health.

Two phenotypes of brain aging were found on analysis: accelerated aging and slower-than-expected aging. The average brain age of participants with the accelerated aging phenotype was 65.1, while the average brain of people with the delayed aging phenotype was 59.7.

Compared to the accelerated aging phenotype, participants with slower or delayed brain aging showed a distinct nutrient profile with higher concentrations of 13 key nutrients including fatty acids (vacenic, gondoic, alpha linolenic, eicosapentaenoic, eicosadienoic, and lignoceric acids), carotenoids cis-lutein, trans-lutein and zeaxanthin, and vitamin E and choline. This nutrient profile correlates with the nutrients in the Mediterranean diet, which has been shown to be beneficial for brain health. The participants who showed this nutrient profile had better scores on cognitive assessments of intelligence, executive function, and memory and exhibited delayed brain aging.

The purpose of this study was to determine nutrient profiles linked to faster or slower aging of the brain. What makes this study unique is that it has combined blood biomarkers, cognitive assessments with validated scales and brain imaging rather than relying on one modality alone. Also, instead of focusing on a single nutrient, it has identified a specific nutrient biomarker profile associated with slower brain aging in participants who showed better cognitive performance.

The demographic and anthropometric factors, including physical fitness had no bearing on the observed differences in brain aging. Therefore, the differences observed can be attributed to the identified nutrient pattern. These findings pave the way for the development of neuroscience-guided dietary interventions to promote

healthy brain aging. The authors conclude by stating that “future research can inform the development of more effective, targeted dietary interventions that apply methods in Nutritional Cognitive Neuroscience”.

## Reference

1. Zwilling CE, et al. Investigating nutrient biomarkers of healthy brain aging: a multimodal brain imaging study. *NPJ Aging*. 2024;10(1):27.

## Gestational Diabetes Pattern and Risk of Incident Diabetes

Women who experience gestational diabetes mellitus (GDM) in the first pregnancy are at a 4.35-fold increased risk of developing new-onset type 2 diabetes compared to women who did not have GDM. This risk increased 7.68-folds if GDM occurred in the second pregnancy only or 15.8-folds in women with a history of GDM in both pregnancies. These findings from a study of nearly half a million women were published May 1, 2024 in *JAMA Network Open*<sup>1</sup>.

This retrospective cohort study aimed to compare the odds of incident diabetes among women with GDM in the first pregnancy, second pregnancy, and in both pregnancies in comparison to women without gestational diabetes in either pregnancy. The Quebec health administrative and birth, stillbirth, and death registries were used to procure data of women who had two singleton deliveries between April 1990 through to December 2012. Data were examined in 2023 between July and December.

The study included 4,31,980 women who had two singleton deliveries; the mean age at the second delivery was 30.1 years, and the mean time elapsed between deliveries was 2.8 years. None of the participants had a history of diabetes. Of these women, 86.4% (n = 3,73,415) were European by heritage, and 18.2% (n = 78,770) belonged to the highest quintile of material deprivation. Over a median follow-up duration of 11.5 years, the incidence of gestational diabetes was 2.5% in the first pregnancy, 3.7% in the second pregnancy and 1.9% in both pregnancies.

Women with GDM only in their first pregnancy had nearly fivefold increased likelihood of developing diabetes with hazard ratio (HR) of 4.35. The risk of future diabetes increased by more than 7.5 times in women with gestational diabetes in their second pregnancy only with HR of 7.68. Among those who had GDM in both pregnancies, the risk of diabetes increased almost 16 times with HR of 15.8.

Gestational diabetes in the second pregnancy increased the hazard of incident diabetes by 76% compared to GDM in the first pregnancy. The risk was increased 3.63-folds in case of gestational diabetes in both pregnancies versus first pregnancy-only gestational diabetes.

This study provides evidence of how GDM occurrence in the first, second, or both pregnancies impacts diabetes risk compared to women with no GDM in either pregnancy. It reveals that gestational diabetes only in the second pregnancy poses a higher risk of incident diabetes than gestational diabetes in the first pregnancy alone. Having GDM in both pregnancies greatly increases the risk of developing diabetes compared to having gestational diabetes in only one pregnancy.

The findings underscore the importance of close monitoring and managing gestational diabetes, especially in subsequent pregnancies, to mitigate the long-term risks of developing diabetes. Not just the number of times of occurrence of GDM, the specific pregnancy affected must also be considered for comprehensive risk assessment and formulating tailored management strategies for better clinical outcomes.

### Reference

1. Mussa J, et al. Incident diabetes in women with patterns of gestational diabetes occurrences across 2 pregnancies. *JAMA Netw Open*. 2024;7(5):e2410279.

### Bronchiectasis Exacerbations and Clinical Outcomes

Patients who have bronchiectasis exacerbations frequently are more likely to have worsening of their disease and experience worse outcomes, according to results of a new research published in the journal *Respiratory Medicine*<sup>1</sup>.

This retrospective cohort study focused on determining the relationship between the number of baseline and follow-up noncystic fibrosis bronchiectasis exacerbations. It also sought to examine how the frequency of exacerbations impacts the longitudinal changes in FEV<sub>1</sub> over time.

Data for the study was obtained from patients enrolled in the US Bronchiectasis and Nontuberculous Mycobacteria Research Registry between September 2008 and March

2020. The relationship between exacerbations at the baseline (24 months) and the 0-to-24 and 24-to-48 month follow-up windows was the outcome of the first objective. Changes in FEV<sub>1</sub> and FEV<sub>1</sub> % anticipated over a 24-month period, stratified by baseline exacerbation frequency, were the outcomes of the second objective.

Around 59.2% of the 520 patients in the first objective cohort, with a mean duration of bronchiectasis of 8.0 years, experienced at least one exacerbation during the baseline period. Around 71.4% of patients who had ≥1 baseline exacerbation experienced ≥1 exacerbation during the 0-to-24 months follow-up. In the 24-to-48 month follow-up, 75.0% of patients who had ≥1 baseline exacerbation experienced ≥1 exacerbation. A significant correlation was seen between having at least one exacerbation at baseline and at least one exacerbation in the 0-to-24 month and 24-to-48 month follow-ups.

The second objective group of 431 patients, with a mean duration of bronchiectasis of 7.7 years, showed a substantially lower FEV<sub>1</sub> at baseline in those with more frequent exacerbations; however, there was no significant difference in the drop in FEV<sub>1</sub> from baseline between patients with 0, 1, and ≥2 exacerbations.

The FEV<sub>1</sub> % predicted at baseline was considerably lower in patients with more exacerbations. And, it continued to remain significantly lower at 12 months and at 24 months in patients with more baseline exacerbations.

This study shows that noncystic fibrosis bronchiectasis patients with a history of frequent exacerbations have worse initial lung function at baseline and are more likely to experience progression of their disease. Prior exacerbations during baseline increased the odds of exacerbations in the next 2 years by 1.5 times and in the following 2 years by 2.4 times," note the authors. "Hence, early identification and aggressive management of patients with frequent exacerbations along with continuous monitoring of lung function is imperative to potentially slow disease progression and the decline in lung function.

### Reference

1. Aksamit TR, et al; Bronchiectasis and NTM Research Registry Investigators. Association between bronchiectasis exacerbations and longitudinal changes in FEV1 in patients from the US bronchiectasis and NTM research registry. *Respir Med*. 2024;228:107660.

