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ABSTRACT & COMMENTARY

The Relationship Among Step Count, Step Intensity, and Mortality in Adults

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

SYNOPSIS: Investigators found an association between higher number of steps taken daily and lower all-cause mortality, lower mortality from cardiovascular disease, and lower mortality from cancer, but no association between intensity of steps and mortality in any of those areas.

SOURCE: Saint-Maurice PF, Troiano RP, Bassett DR, et al. Association of daily step count and step intensity with mortality among U.S. adults. *JAMA* 2020;323:1151-1160.

In a 1786 letter to his son-in-law, Thomas Jefferson wrote, "I have known some great walkers and had particular accounts of many more; and I never knew or heard of one who was not healthy and long lived."[1] More than 200 years later, Saint-Maurice et al have used research methods from 2020 to understand and delineate the relationship among walking, health, and longevity long ago noted by one of the United States' "founding fathers."

Saint-Maurice et al noted the lack of evidence-based studies supporting the popular goal of achieving 10,000 steps each day. Prior investigations involving walking and health have affirmed the health benefits of walking, but typically involved limited and specific populations.[2,3] Therefore, findings are not necessarily applicable to other groups or to a more general population. In addition, there have been conflicting results in studies of step intensity and association with health benefits.[4,5] Citing these reasons, this team set out to look at any association between step count, step intensity, and mortality in a representative sample of the U.S. population older than age 40 years.

The National Health and Nutrition Examination Survey (NHANES), a Centers for Disease Control and Prevention-sponsored program, annually collects data from a nationally representative sample of the U.S. population.[6] From 2003 to 2006, 4,840

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respondents aged 40 years or older from NHANES wore standardized hip accelerometers during a seven-day period. Saint-Maurice et al used data from the accelerometers to determine participant step count and step intensity. Considering the breadth of information collected by NHANES, the team adjusted results for a variety of factors, including age, education, substance use, specific medical diagnosis, and self-reported general health. There were 6,355 respondents initially eligible for inclusion in the study, but there were sufficient data for only 4,840 people; 1,515 individuals either elected not to wear the accelerometer or did not submit a record for at least one 12-hour period. The authors accessed the National Death Registry periodically until Dec. 31, 2015, to determine death of any participant from any cause. Indications that a participant had died by either cancer or cardiovascular disorder were noted, too.

The mean number of steps/day for the entire group of 4,840 participants was 9,124. The mean length of time wearing the accelerometer was 5.7 days, while the mean time each day was 14.4 hours. Respondent data were stratified according to number of daily steps:

- < 4,000 steps/day (n = 655)
- 4,000-7,999 steps/day (n = 1,727)
- 8,000-11,999 steps/day (n = 1,539)
- > 12,000 steps/day (n = 919)

Considering the differences between the groups, and an analysis showing significant attenuation of results with adjustment for some variables, Saint-Maurice et al presented several interpretive models for review and discussion. In addition to all-cause mortality, the authors examined death as the result of cardiovascular disease and cancer. Each revealed a similar pattern of a significant decrease in mortality rate with increasing step count. In addition, results indicated consistent findings: decelerated mortality rate with more steps taken when reported separately for men, women, age groups, and ethnicity.

The second major part of this study concerned step intensity and mortality rate (MR). Step intensity was calculated in several manners (based on time and number of steps). Higher step intensity was associated with significantly lower MR — until adjusting these figures for number of steps daily. For example, the unadjusted MR was 5.2 (95% confidence interval [CI], 3.2-7.3) per 1,000 adults/year for those in the highest quadrant of step intensity and 10.0 (95% CI, 7.1-12.9) for the respondents on the other end of the scale. However, when adjusting for the number of steps in both quadrants, this difference virtually vanishes, with an adjusted MR of 8.4 (95% CI, 4.0-12.9) per 1,000 adults/year and 9.2 (95% CI, 6.9-11.8) per 1,000 adults/year. The *P* value for the trend is 0.34.

■ COMMENTARY

This study gives backbone to the principle of viewing physical activity as essential "medicine" for health. The association between step count and longevity found by Saint-Maurice et al is consistent with studies of step count and health both in investigations centered on older adults and in studies of persons with chronic illnesses.[2,3] This work adds to the literature by generalizing the findings from these narrower studies and pointing toward a dose relationship between step count and longevity.

It is important to note this was an observational study; there is no evidence for causation. There are some other significant limitations, including the fact the participant group was self-selected, and that wearing the accelerometer itself may have produced an effect (such as motivating more walking or motivating a more active lifestyle). Future investigations with randomization and controls will be helpful in further understanding and quantifying the relationship between step count and longevity.

It is notable that even when adjusted for a substantial number of variables, results still indicate a dose-response relationship between step count and longevity, with hazard ratio indicating a 65% reduced chance of death among the group taking 12,000 or more steps daily when compared to the referent group (taking 4,000 steps or fewer daily). The authors of future investigations may want to look more closely at the lifestyle of the most active group to see if there are other variables influencing longevity, such as

participation in activities that may not register on an accelerometer (e.g., biking or swimming). Another point to consider is that the only accelerometer data came from a seven-day period between 2003 and 2006. There is little evidence to suggest this period is representative of a respondent's lifestyle in general and/or over time. More information and data from subsequent years will be helpful in evaluating whether accelerometer patterns stay stable over time and ultimately may help in attempts to address the question of causation. The investigators expected to see an association of step intensity with mortality, and were surprised at not finding this relationship. They noted there has been only a smattering of studies of the effect of step intensity on mortality and suggested further studies to understand this in full. In this paper, it appears that step intensity is associated with greater number of steps in general. Even with the limitations noted, the Saint-Maurice et al study represents a true "step" forward in the field. While it is prudent to wait for evidence of causation, there is no need to wait for recommending an active lifestyle to patients. Today, many patients wear devices that measure not only step count, but also many other health parameters associated with activity, including heart rate and recovery time. Using these devices and active monitoring may become an integral component of a modern wellness plan. We know activity is helpful for many health measures and conditions, including reducing the risk of type 2 diabetes, obesity, and heart disease. This study strengthens the argument for continuing to keep physical activity as the foundation of a healthy lifestyle and adds evidence to a role for physical activity in longevity. ■

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BRIEF REPORT

Stroke Risk: COVID-19 vs. Influenza

By Matthew E. Fink, MD

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

SOURCE: Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID–19) vs patients with influenza. *JAMA Neurol* 2020; July 2. doi:10.1001/jamaneurol.2020.2730. [Online ahead of print].

Early in the COVID-19 pandemic, reports emerged from China and France that there might be an increased risk of ischemic stroke. Many patients developed a hypercoagulable state with thrombotic complications in multiple organs, including the lungs, kidneys, heart, liver, and brain. During the

surge in COVID-19 infections in New York City, many neurologists observed an unusual frequency of ischemic stroke.

Merkler and colleagues designed a retrospective cohort study of patients admitted with COVID-19 infection, confirmed by polymerase chain reaction testing by a nasal swab, from March 4, 2020, through May 2, 2020. They identified all acute strokes, and compared them with a matched group of patients hospitalized with influenza A and B from January 2016 through May 2018. It is well documented that influenza epidemics are associated with a higher risk of ischemic stroke and myocardial infarction, as are all systemic inflammatory disorders. Merkler and colleagues wanted to determine if coronavirus infection induced a higher risk of ischemic stroke than other viral infections, such as influenza.

A total of 1,916 patients with documented COVID-19 infection were admitted to the hospital, and 31 suffered an acute ischemic stroke during their hospitalization (95% confidence interval [CI], 1.1%-2.3%). The median age was 69 years, and 58% were men. Eight patients presented to the hospital with stroke as their chief complaint.

Of 1,486 patients with influenza, only three suffered an acute ischemic stroke during hospitalization (95% CI, 0.0%-0.6%). After adjustment for demographic factors, age, sex, and race, the probability of stroke was higher with COVID-19 infection than with influenza infection (odds ratio, 7.6; 95% CI, 2.3-25.2). This high rate of ischemic stroke is consistent with reports from other centers in New York City, as well as in cities around the world that have reported their findings.

The observed thrombotic events likely are the cause for the high rate of ischemic stroke in these patients and should be addressed aggressively as part of a comprehensive treatment plan. Right now, it is unknown what the long-term consequences will be in this population. Regardless, it is likely there will be a high rate of physical disabilities and neurological disabilities. ■

BRIEF REPORT

Risks of Hookah Smoking

By Carol A. Kemper, MD, FACP

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

SOURCE: International Society for Infectious Diseases. ProMED-Mail. Tuberculosis — Switzerland: Hookah usage. Dec. 27, 2019. https://bit.ly/2BWn3bZ

Smoking a hookah pipe is a centuries-old social custom in some societies. A pipe filled with "shisha," or flavored tobacco, is passed around in a group, sometimes for hours, often at a hookah cafe. The same mouthpiece is shared, and the device may or may not be cleaned well between uses. Dried tobacco is combined with fruit pulp, molasses, and/or honey — or other flavorings such as coconut, mint, or coffee. This lends a sweet quality to the smoke, which, when drawn through a water bath, gives the impression to many that smoking a hookah is safer than smoking cigarettes.

Apparently, this is not the case. The water bath may diminish the tar from charcoal-burned tobacco, but that bath does not filter many of the cancer-causing chemicals, hydrocarbons, and metals found in today's tobacco. And it is not just the chemicals: An average hookah contains as much tobacco as 20 filtered cigarettes. The nicotine hit from a hookah is every bit as real — and as addictive — as smoking cigarettes. Further, the temperature of the smoke when heated electronically in newer hookahs, rather than by older charcoal versions, may be cidal to lung cells.

The authors of a recent University of California study found that one good draw on a hookah was similar to smoking one filtered cigarette in terms of hazardous chemicals and metals. Further, the amount of carbon monoxide inhaled during one hookah session was similar to smoking 12 cigarettes.

Another adverse effect from sharing a hookah is the spread of oral and respiratory infections, such as herpes simplex, syphilis, and tuberculosis. While the water bath may filter larger particles, it actually creates ultra-fine particles that can pass directly to the deeper parts of the lungs. Some extra-fine particles (< 0.1 micron) may pass directly through lung tissue into the bloodstream. The authors of this Pro-MED-

Mail report identified a 20-year-old man with cavitary tuberculosis (TB). He was a regular hookah smoker, and smoked at least five times per week with friends. The authors theorized regular hookah smoking increased his risk for TB, with close, high-level contact, and spread of microparticles from the mouthpiece. Alternately, frequenting hookah cafés, crowded with people smoking and coughing, also could increase the risk for TB exposure. One wonders if the hot smoke may increase the risk of more severe bacterial or viral lung infection via repeated damage or inflammation to the tissues, similar to vaping. ■

ABSTRACT & COMMENTARY

Cheyne-Stokes Respiration in Heart Failure

By Michael H. Crawford, MD

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

SYNOPSIS: A comprehensive cardiorespiratory study of stable systolic heart failure patients showed Cheyne-Stokes breathing in the awake, upright position is related to hypercapnia and is independently associated with a higher risk of cardiac death.

SOURCE: Giannoni A, Gentile F, Sciarrone P, et al. Upright Cheyne-Stokes respiration in patients with heart failure. *J Am Coll Cardiol* 2020;75:2934-2946.

Supine or sleeping Cheyne-Stokes respiration (CSR) in heart failure subjects is known to be associated with increased severity of disease and a poor prognosis. Less is known about daytime, upright CSR.

Giannoni et al enrolled stable systolic heart failure patients on optimal guideline-based therapy between 2007 and 2018. Those with other comorbidities or on drugs that influence respiratory control were excluded. Each patient underwent two days of intensive baseline testing for cardiopulmonary and neurohormonal characterization. Apnea was defined as cessation of airflow lasting ≥ 10 seconds. Hypopnea was defined as a reduction in airflow ≥ 50% lasting ≥ 10 seconds in association with reduced oxygen saturation (≥ 4% during a 24-hour ambulatory polygraphic cardiorespiratory recording). The authors used the rebreathing technique to assess chemoreflex sensitivity to hypoxia and hypercapnia. Also, researchers performed short-term respiratory response to head up tilt testing. Patients were classified as normal breathing, supine CSR, or upright CSR. Among the 574 patients enrolled, 297 breathed normally, 195 were classified as supine CSR, and 82 were classified as supine and upright CSR.

Compared to those who breathed normally, patients with upright CSR recorded significantly lower ventricular ejection fraction, larger left atria, higher systolic pulmonary artery pressures, higher norepinephrine levels, and higher NT-pro BNP levels. They also recorded lower peak VO_2 levels, more oscillatory exercise breathing, a higher ratio of ventilation to CO_2 output, more atrial fibrillation, and more moderate to severe mitral regurgitation. In addition, they scored higher on the apnea-hypopnea index and central apnea index vs. normal breathing patients and those classified as supine CSR only.

Using a multivariate logistic analysis, the only independent predictor of upright CSR was hypercapnic ventilatory response (hazard ratio [HR], 4.01; 95% confidence interval [CI], 1.54-10.46; $P = 0.004$). After an eight-year follow-up, upright CSR was independently predictive of a higher risk of cardiac death (HR, 2.39; 95% CI, 1.08-5.29; $P = 0.032$), as was moderate to severe mitral regurgitation (HR, 3.82). The authors concluded upright CSR is related to an increased sensitivity to hypercapnia, is associated with more severe disease, and is associated with a greater risk of cardiac death.

■ COMMENTARY

CSR has long been recognized as a useful bedside observation to confirm the severity of heart failure. The authors of older studies have noted an inverse association between the total cycle length, not just the apnea time, and cardiac output. In more recent studies, investigators have noted CSR is frequent in heart failure patients during polysomnographic studies, categorizing it as a rhythmic subtype of central sleep apnea. It occurs in about half of stable heart failure patients and is associated with a higher risk of ventricular tachycardia and death.

Giannoni et al explored the observation that CSR can occur while awake and even during exercise. They used a simple polygraph to detect CSR in upright patients. They started with 15 minutes of rest. If CSR was observed, they moved on to 15 minutes of

head-up tilt. This maneuver uncovered upright CSR in 14% of their patients. These patients featured a worse adrenergic and hemodynamic profile, with the highest levels of norepinephrine, NT-pro BNP, atrial fibrillation, moderate to severe mitral valve regurgitation, and eight-year cardiac mortality. CSR was considered sleep related because the cortical influences on respiration would diminish during sleep, allowing the chemical control of breathing to dominate. Also, fluid redistribution to the lungs while sleeping could exacerbate the problem.

Obstructive sleep apnea almost always is sleep related, but CSR also can occur during awake daylight time. The mechanism of upright CSR is not completely clear. In the Giannoni et al study, the only predictor of upright CSR was chemosensitivity to increased CO_2, but there may be other contributors. Other studies have shown a relationship between left atrial pressure (LAP) and supine CSR. Perhaps upright positioning reduces LAP and prevents upright CSR in many stable heart failure patients. Upright CSR patients in the Giannoni et al study had more severe mitral regurgitation. Perhaps this maintained high atrial pressures upright.

The major limitation of this study is that CSR was assessed only once at intake. There could have been changes in CSR status over the eight-year follow-up. What are the clinical implications of this study? Upright CSR could be detected easily in an office practice and would be of prognostic value. Should the detection of CSR drive more aggressive therapy? Studies of correcting CSR associated with sleep apnea in heart failure patients indicate that such correction was not effective at improving outcomes. At this point, there is no specific therapy occasioned by the detection of upright CSR. ■

PHARMACOLOGY UPDATE

Decitabine and Cedazuridine Tablets (Inqovi)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The Food and Drug Administration has approved an oral fixed-combination medication for the treatment of adults with myelodysplastic syndromes (MDS). The combination is comprised of decitabine, a nucleoside metabolic inhibitor/hypomethylating agent, and cedazuridine, a cytidine deaminase (CDA) inhibitor. Inhibition of CDA reduces the degradation of decitabine in the gastrointestinal tract and liver-preserving oral bioavailability. Before this combination, decitabine was given by intravenous (IV) infusion over three or five days, which required a visit to a healthcare facility. Decitabine and cedazuridine (DEC/CED) received priority review and fast-track breakthrough therapy designations. It is distributed as Inqovi.

INDICATIONS

DEC/CED should be prescribed to treat adult patients with MDS. This includes previously untreated and treated de novo and secondary MDS with the following French-American-British subtypes: chronic myelomonocytic leukemia (CMML); intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups; and refractory anemia, refractory anemia with excess blasts, and refractory anemia with ringed sideroblasts.[1]

DOSAGE

The recommended dose is one tablet orally once daily on days 1 through 5 of each 28-day cycle at the same time each day on an empty stomach.[1] Food should not be ingested two hours before or two hours after each dose. Dose reduction/modification is recommended for myelosuppression, elevation of serum creatinine, serum bilirubin, liver enzymes, or active or uncontrolled infections.[1] Each tablet contains 35 mg of DEC and 100 mg of CED.

POTENTIAL ADVANTAGES

This oral formulation provides a much more convenient administration compared to the IV infusion that necessitated a visit to a healthcare facility for administration. The systemic exposure of DEC/CED after five consecutive once-daily dosing days is comparable to that of IV DEC, with a cumulative mean ratio of area under the plasma time curve of 99% (90% confidence interval, 93-106).[1]

POTENTIAL DISADVANTAGES

The frequencies of adverse reactions generally were similar between DEC/CED and IV DEC.[1] In clinical trials, 5% of subjects permanently discontinued the drug because of adverse reactions, 41% reported dose

interruptions, and 19% experienced dose reduction.[1] Serious and fatal adverse reactions with DEC/CED are related to myelosuppression, such as Grade 3 and 4 thrombocytopenia (76%), neutropenia (73%), and anemia (71%).[1]

COMMENTS

Aberrant DNA methylation is a possible mechanism of pathogenesis in MDS. DEC is a hypomethylating agent because it inhibits DNA methyltransferase.[1] DEC/CED was compared to IV DEC in two open-label, randomized, two-cycle, two-sequence, crossover studies.[1,2] In both studies, subjects with MDS or CMML (n = 80; n = 133) were randomized to DEC/CED or IV DEC (20 mg/m^2) in cycle 1 and the reverse for cycle 2 for days 1 through 5 of each 28-day cycle. Starting with cycle 3, all subjects took DEC/CED until disease progression or unacceptable toxicity. Pharmacokinetics and pharmacodynamic assessments were observed in the intrasubject crossover cycles 1 and 2. The two formulations showed comparable systemic exposure and in percent change in demethylation from baseline. Clinical response was based on complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence, starting with cycle 3.

In the first study, after a median duration of treatment of 6.6 months and median follow-up time of 24 months, CR rate was 18%, with a median duration of 8.7 months and median time to CR of 4.8 months. Twenty of 41 subjects who were red blood cell- and/or platelet transfusion-dependent were transfusion-independent in any 56-day post-baseline period. Sixty-four percent of those who were transfusion-independent remained transfusion-independent.

In the second study, the CR rate was 21%, with a median duration of CR of 7.5 months and median time to CR of 4.3 months. Thirty of 57 transfusion-dependent subjects became transfusion-independent, and 48 of 76 remained transfusion-independent. CR rates were similar to those reported for the IV formulation.[3,4]

CLINICAL IMPLICATIONS

MDS is a group of blood and bone marrow disorders that is considered a form of cancer.[5,6] It is characterized by stem cells not maturing properly, resulting in immature and abnormally developed cells in the circulation, with fewer normal healthy red cells, white cells, and/or platelets. There are seven subtypes, with some subtypes progressing to acute myeloid leukemia. The National Comprehensive Cancer Network recommends azacitidine or DEC for most patients with clinically relevant thrombocytopenia or neutropenia or increased marrow blasts. Both require parenteral administration with DEC, which requires IV infusion over one to three hours with monthly, multiple-day administrations.

DEC/CED provides an oral option for a drug that requires long-term administration with comparable pharmacokinetic and pharmacodynamic assessments and with clinical responses consistent with IV DEC. Hypomethylating agents, such as DEC, result in a 40% to 50% response rate, with 10% to 20% complete response.[4] The responders also tend to experience disease progression with loss of response over time.[4] Therefore, new treatment options still are needed. The cost for DEC/CED was unavailable at the time of this review. ■

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CME QUESTIONS

1. **In the Saint-Maurice et al study, taking more steps each day was:**
   a. associated with decreased mortality until a plateau of 10,000 steps daily at a rapid rate; over this level did not seem to provide further, measurable health benefits.
   b. associated with decreased mortality in a dose-response pattern; evidence of a link between walk intensity and mortality diminished when adjusted for daily step count.
   c. associated with decreased mortality until a plateau of 10,000 steps daily at any rate (slow to rapid); over this level did not seem to provide further, measurable health benefits.
   d. associated with decreased mortality in a dose-response pattern; evidence of a link between walk intensity and mortality is suggested from this study as well, but the pattern is not as linear and may plateau at moderate walk intensity.

2. **COVID-19 is associated with multiple thrombotic complications, including a high rate of ischemic stroke.**
   a. True
   b. False

3. **Cheyne-Stokes respiration in stable systolic heart failure patients is related to increased sensitivity to:**
   a. hypoxia.
   b. hypercapnia.
   c. acidosis.
   d. exercise VO_2 maximum.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.