Group 1 papers to be discussed in Class 8 (2021-03-25)

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Analysis of Effects of Agriculture Intervention Using Propensity Score Matching

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Abstract

Nowadays, the agriculture extension programmes are practiced in many parts of the world. There is a mixture of results about the effects of agriculture intervention programmes. The literature shows that the interventions are ineffective and have limited diffusion. On the other side, it shows that interventions are effective. Following different arguments about the effects of agriculture extension, this paper adopted Propensity Score Matching (PSM) to analyze the effects of District Agricultural Sector Investment Project (DASIP) using agriculture data.

The study was conducted in rural Tanzania areas. It covered five regions namely Kagera, Mwanza, Mara, Simiyu and Kigoma. The study focused on agro-ecological zone where corn is cultivated. Two methods which are questionnaire administration and direct oral interview were used to collect primary data. The collection of data using the questionnaire was done from both participants (359) and non-participants (519). Before running the independent t test, the estimation of propensity score was done using Logistic regression. Thirteen confounding variables were used to estimate propensity scores.

The effects of the intervention were analysed by considering four items namely the earnings from corn production, value of livestock owned, value of household assets owned, and value of farm assets owned. The results show that none of the four factors had significant result as the p values are greater than 0.05. This implies that the earning between farmers participating in DASIP are not significant different from those who do not participate in the programme. The study recommends that the group activities should last longer rather than changing them from time to time.

Keywords: Agriculture Extension programme, DASIP, Farmer Field School, Intervention, Propensity Score Matching (PSM)

1. Introduction

The agriculture plays a major role in economic development (Yeshwanth, 2008). Nowadays, agriculture extension programmes are practiced in many parts of the world. Such programmes are implemented because farmers lack direct linkage with advanced agricultural technology. It is through extensions where farmers are given knowledge, skills and motivation for farming. These are done through Farmer Field Schools (FFS) also called Participatory Group Farmers (PGFs) model.

The FFS started in Tanzania in the 1997 (Braun et al., 2006). The approach has been engineered by both government and non-governmental organizations. The government of Tanzania adopted the FFS approach in one of its project called District Agricultural Sector Investment Project (DASIP) in which this paper is focused. The DASIP is a six year project aimed at increasing the productivity and incomes of rural households in the project area within the overall framework of the Agricultural Sector Development Strategy (ASDS). The DASIP started in the 2006.

One of the main challenges that the extension and research is currently confronted with is the transfer of agricultural technology from the research stations to the farm lands (Dinpanah et al., 2010). There is a mixture of results about the effects of agriculture intervention programmes. The literature shows that the interventions are ineffective and have limited diffusion (see Quizon et al., 2001; Feder et al., 2003; and Rola et al., 2002). On the other side, the literature shows that FFS are effective (see Godtland et al., 2004; Van den Berg., 2004; Feder et al., 2003; Tripp et al, 2005; Erickson, 2003; and Ooi et al, 2005).

There is less common rigorous impact evaluations of agricultural extension interventions despite the vast literature dealing with issues related to agricultural extension (Waddington et al., 2010). Heinrich et al. (2010) argue that this is a result of several problems accompanied by the evaluation of the programmes. The problems include: establishing the counterfactual; need for an adequate comparison group; selection bias; and role of randomization (Duflo and Kremer, 2003). These problems can be solved by the use of statistical methods depending on the nature of the intervention programmes. Unfortunately, the data used in the past impact analyses did not define well the counterfactual factors. The comparison is done by just looking at two observation points that is, before and after.

The intervention programmes can either be random or non-random. The randomized design

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Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: A propensity matched analysis

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ABSTRACT

Introduction: Obesity is a risk factor for non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). Bariatric surgery can provide durable weight-loss, but little is known about the later development of NASH and HCC after surgery.

Methods: Bariatric surgery (n = 3,410) and obese controls (n = 46,873) from an institutional data repository were propensity score matched 1:1 by demographics, comorbidities, BMI, and socioeconomic factors. Comparisons were made through paired univariate analysis and conditional logistic regression.

Results: Total of 4,112 patients were well matched with no significant baseline differences except initial BMI (49.0 vs 48.2, $p = 0.04$). Bariatric group demonstrated fewer new-onset NASH (6 0.0% vs 10.3%, $p < 0.0001$) and HCC (0.05% vs 0.34%, $p = 0.03$) over a median follow-up of 7.1 years. After risk-adjustment, bariatric surgery was independently associated with reduced development of NASH (OR 0.52, $p < 0.0001$).

Conclusions: Bariatric surgery is associated with reduced incidence of NASH and HCC in this large propensity matched cohort. This further supports the use of bariatric surgery for morbidly obese patients to ameliorate NASH cirrhosis and development of HCC.

Introduction

Incidences of non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) are increasing throughout the United States.[1,2] A large contributing factor may be the rise of obese adults, as this trend is increasingly affecting adolescents, as well. The progression of NASH from non-alcoholic fatty liver disease (NAFLD) occurs in approximately 10–25% of patients[3] and can lead to significant risks in liver-related mortality due to the development of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). It is projected that more than 10% weight loss is needed in order to improve NASH,[4] however, weight loss modification through lifestyle changes alone account for only 3–5% total body weight loss on average and does not provide durable weight loss over time.[5] Two first-line medications (Vitamin E and pioglitazone) have been used to augment this effect,[6] however there are concerns due their association with other cancers and morality risk, also in their lack of improving hepatic fibrosis.[7] Additionally, the effectiveness of these medications was only studied in non-diabetic patients which leaves limited options for the greater proportion of obese patients that are also diabetic.

Bariatric surgery has shown to provide sustained weight loss throughout the course of a patient's lifetime,[8] and most patients who are candidates for bariatric surgery have some degree of NAFLD.[6] Previous studies have shown that bariatric surgery not only improves steatosis in NASH, but may also improve hepatic fibrosis even in patients who may have other metabolic diseases including diabetes mellitus type II (DM2).[5,7,9,10] However, this was not a consistent finding since a few studies also showed worsening hepatic fibrosis over time.[5,7,9–11] It is due to this concern that despite guidelines suggesting the benefit of bariatric surgery in reducing the progression to NASH, there is still no definitive recommendation on its routine use.[6,11] This may, in part, have contributed to the overall decrease in the number of bariatric

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RESEARCH

Association of delay of urgent or emergency surgery with mortality and use of health care resources: a propensity score–matched observational cohort study

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ABSTRACT

BACKGROUND: Delay of surgery for hip fracture is associated with increased risk of morbidity and mortality, but the effects of surgical delays on mortality and resource use in the context of other emergency surgeries is poorly described. Our objective was to measure the independent association between delay of emergency surgery and in-hospital mortality, length of stay and costs.

METHODS: We identified all adult patients who underwent emergency noncardiac surgery between January 2012 and October 2014 at a single tertiary care centre. Delay of surgery was defined as the time from surgical booking to operating room entry exceeding institutionally defined acceptable wait times, based on a standardized 5-level priority system that accounted for surgery type and indication. Patients with delayed surgery were matched to those without delay using propensity scores derived from variables that accounted for details of admission and the hospital stay, patient characteristics, physiologic instability, and surgical urgency and risk.

RESULTS: Of 15 160 patients, 2820 (18.6%) experienced a delay. The mortality rates were 4.9% (138/2820) for those with delay and 3.2% (391/12 340) for those without delay (odds ratio [OR] 1.59, 95% confidence interval [CI] 1.30–1.93). Within the propensity-matched cohort, delay was significantly associated with mortality (OR 1.56, 95% CI 1.18–2.06), increased length of stay (incident rate ratio 1.07, 95% CI 1.01–1.11) and higher total costs (incident rate ratio 1.06, 95% CI 1.01–1.11).

INTERPRETATION: Delayed operating room access for emergency surgery was associated with increased risk of in-hospital mortality, longer length of stay and higher costs. System issues appeared to underlie most delays and must be addressed to improve the outcomes of emergency surgery.

Patients undergoing emergency surgery are at high risk of adverse outcomes.[1] Although patient characteristics[2,3] and surgical indication[4,5] are the most important risk factors, system factors, such as delayed access to the operating room, also affect outcomes. In hip fracture surgery, delay is associated with morbidity and mortality,[6,7] but for other surgeries, the effect of delay on outcomes is unclear.[8–13] Because it is very expensive to expand or reorganize operating room resources to improve access,[14–16] understanding the relation between delay and outcomes for all types of emergency surgery is needed.

The association between surgical delay and outcome may be obscured by confounding. The indication for surgery, comorbidities and physiologic disturbances may influence both the risk of delay and the risk of adverse outcomes. Furthermore, ascertainment of delay is a challenge. Many studies measure surgical wait time as the time from admission to surgery, but this is misleading, because inpatient work-up is often required to determine the risks and potential benefits of surgery.

The purpose of this study was to determine the independent association of surgical delay with inpatient mortality, postoperative length of stay and total costs of hospital care.

Differences in sexually transmitted infection risk comparing preexposure prophylaxis users and propensity score matched historical controls in a clinic setting

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Objective: The aim of this study was to determine whether MSM using preexposure prophylaxis (PrEP) are at a higher risk of bacterial sexually transmitted infections (STIs) than MSM not using PrEP.

Design: Secondary analysis of longitudinal STI data obtained from MSM attending an STD Clinic in Seattle, Washington, USA, October 2011–September 2017.

Methods: We identified patients obtaining PrEP through the STD Clinic, and used propensity score matching to select a historical group of similar patients not using PrEP for comparison. We linked patient data with STI surveillance data to compare the incidence of chlamydia, gonorrhoea and early syphilis, and time to first symptomatic STI among PrEP users and nonusers.

Results: Three hundred and sixty-five PrEP users who picked up prescriptions and returned for follow-up and 730 propensity score matched nonusers were included in the analysis. Adjusted incidence rate ratios (aIRRs) for chlamydia, gonorrhoea and early syphilis were 3.2 [95% confidence interval (95% CI): 1.9–5.3], 2.8 (95% CI: 1.7–4.6) and 2.9 (95% CI: 1.5 – 5.6), respectively, comparing PrEP users to nonusers. Time to first symptomatic STI was shorter among PrEP users (120 days, 95% CI: 77 – 171) than among nonusers (185 days, 95% CI: 163–256).

Conclusion: Among MSM on PrEP, we observed a higher incidence of STIs and faster time to first symptomatic STI than MSM not using PrEP. PrEP may be a contributing factor in increasing STI rates among MSM.

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Keywords: HIV, MSM, preexposure prophylaxis, sexually transmitted infections

Introduction

MSM are disproportionately impacted by HIV in the United States, accounting for 86% of new infections among men in 2016 [1]. Preexposure prophylaxis (PrEP) reduces the risk of HIV acquisition by up to 92% in MSM [2–4], is recommended by the Centers for Disease Control and Prevention (CDC) for HIV prevention among sexually active MSM [5] and is offered through a variety of clinical settings in the U.S. [6]. MSM are also

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Association of Rituximab Treatment With Disability Progression Among Patients With Secondary Progressive Multiple Sclerosis

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IMPORTANCE Therapeutic options for patients with secondary progressive multiple sclerosis (SPMS) are limited.

OBJECTIVE To analyze disability progression in patients with SPMS treated with rituximab compared with matched control patients never treated with rituximab.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study analyzed data obtained from patients with SPMS at 3 multiple sclerosis centers located in Basel and Lugano, Switzerland, and Amsterdam, the Netherlands, from 2004 to 2017. Patients were included for analysis if they had received a diagnosis of SPMS, were treated (57 eligible; 54 included) or never treated (504 eligible; 59 included) with rituximab, and had at least 1 follow-up visit. The variables used for propensity score matching were sex, age, Expanded Disability Status Scale (EDSS) score, and disease duration. Follow-up duration was up to 10 years, with a mean (SD) of 3.5 (2.6) years for rituximab-treated patients and 5.4 (2.4) years for controls in the total cohort and a mean (SD) of 3.5 (2.7) years for rituximab-treated patients and 4.8 (2.2) years for controls in the matched cohort.

EXPOSURES Comparing EDSS score progression in patients with SPMS (treated with rituximab vs not treated with rituximab) using propensity score matching.

MAIN OUTCOMES AND MEASURES The primary end point was progression of EDSS score after baseline, and the secondary end point was time to confirmed disability progression.

RESULTS After 1:1 propensity score matching, 44 matched pairs (88 patients) were included in the analysis. At baseline, patients treated with rituximab had a mean (SD) age of 49.7 (10.0) years, mean (SD) disease duration of 18.2 (9.4) years, and mean (SD) EDSS score of 5.9 (1.4), and 26 (59%) were women, whereas controls had a mean (SD) age of 51.3 (7.4) years, mean (SD) disease duration of 19.4 (8.7) years, and mean (SD) EDSS score of 5.70 (1.29), and 27 (61%) were women. In the covariate-adjusted analysis of the matched set, patients with SPMS who were treated with rituximab had a significantly lower EDSS score during a mean (SD) follow-up of 3.5 (2.7) years (mean difference, −0.52; 95% CI, −0.79 to −0.26; $P < .001$). Time to confirmed disability progression was significantly delayed in the rituximab-treated group (hazard ratio, 0.49; 95% CI, 0.26-0.93; $P = .03$).

CONCLUSIONS AND RELEVANCE In this study, patients with SPMS treated with rituximab had a significantly lower EDSS score for up to 10 years of follow-up and a significantly delayed confirmed progression compared with matched controls, suggesting that B-cell depletion by rituximab may be therapeutically beneficial in these patients. A prospective randomized clinical trial with a better level of evidence is needed to confirm the efficacy of rituximab in such patients.

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Supplemental content

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Group 2 papers to be discussed in Class 9 (2021-04-01)

Branigan
Eshleman
Waibel

JAMA Network Open

Original Investigation | Neurology

Association Between Hormone-Modulating Breast Cancer Therapies and Incidence of Neurodegenerative Outcomes for Women With Breast Cancer

Gregory L. Branigan, BS; Maira Soto, PhD; Leigh Neumayer, MD, MS; Kathleen Rodgers, PhD; Roberta Diaz Brinton, PhD

Abstract

IMPORTANCE The association between exposure to hormone-modulating therapy (HMT) as breast cancer treatment and neurodegenerative disease (NDD) is unclear.

OBJECTIVE To determine whether HMT exposure is associated with the risk of NDD in women with breast cancer.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used the Humana claims data set from January 1, 2007, to March 31, 2017. The Humana data set contains claims from private-payer and Medicare insurance data sets from across the United States with a population primarily residing in the Southeast. Patient claims records were surveyed for a diagnosis of NDD starting 1 year after breast cancer diagnosis for the duration of enrollment in the claims database. Participants were 57 843 women aged 45 years or older with a diagnosis of breast cancer. Patients were required to be actively enrolled in Humana claims records for 6 months prior to and at least 3 years after the diagnosis of breast cancer. The analyses were conducted between January 1 and 15, 2020.

EXPOSURE Hormone-modulating therapy (selective estrogen receptor modulators, estrogen receptor antagonists, and aromatase inhibitors).

MAIN OUTCOMES AND MEASURES Patients receiving HMT for breast cancer treatment were identified. Survival analysis was used to determine the association between HMT exposure and diagnosis of NDD. A propensity score approach was used to minimize measured and unmeasured selection bias.

RESULTS Of the 326 485 women with breast cancer in the Humana data set between 2007 and 2017, 57 843 met the study criteria. Of these, 18 126 (31.3%; mean [SD] age, 76.2 [7.0] years) received HMT, whereas 39 717 (68.7%; mean [SD] age, 76.8 [7.0] years) did not receive HMT. Mean (SD) follow-up was 5.5 (1.8) years. In the propensity score–matched population, exposure to HMT was associated with a decrease in the number of women who received a diagnosis of NDD (2229 of 17 878 [12.5%] vs 2559 of 17 878 [14.3%]; relative risk, 0.89; 95% CI, 0.84-0.93; $P < .001$), Alzheimer disease (877 of 17 878 [4.9%] vs 1068 of 17 878 [6.0%]; relative risk, 0.82; 95% CI, 0.75-0.90; $P < .001$), and dementia (1862 of 17 878 [10.4%] vs 2116 of 17 878 [11.8%]; relative risk, 0.88; 95% CI, 0.83-0.93; $P < .001$). The number needed to treat was 62.51 for all NDDs, 93.61 for Alzheimer disease, and 69.56 for dementia.

CONCLUSIONS AND RELEVANCE Among patients with breast cancer, tamoxifen and steroidal aromatase inhibitors were associated with a decrease in the number who received a diagnosis of NDD, specifically Alzheimer disease and dementia.

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Key Points

Question Is hormone-modulating therapy associated with neurodegenerative disease in women with breast cancer?

Findings In this cohort study of 57 843 perimenopausal- to postmenopausal-aged women with breast cancer, exposure to hormone-modulating therapy (tamoxifen and aromatase inhibitors, especially exemestane) was associated with a significant decrease in the number of women who received a diagnosis of neurodegenerative disease, most specifically Alzheimer disease.

Meaning With the increased life expectancy seen after treatment, therapy selection for breast cancer should include a careful discussion of the risks and benefits of each treatment option that may be associated with a reduced risk of neurodegenerative disease.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Do Big 4 Auditors Provide Higher Audit Quality after Controlling for the Endogenous Choice of Auditor?

John Daniel Eshleman and Peng Guo

SUMMARY: Recent research suggests that Big 4 auditors do not provide higher audit quality than other auditors, after controlling for the endogenous choice of auditor. We re-examine this issue using the incidence of accounting restatements as a measure of audit quality. Using a propensity-score matching procedure similar to that used by recent research to control for clients' endogenous choice of auditor, we find that clients of Big 4 audit firms are less likely to subsequently issue an accounting restatement than are clients of other auditors. In additional tests, we find weak evidence that clients of Big 4 auditors are less likely to issue accounting restatements than are clients of Mid-tier auditors (Grant Thornton and BDO Seidman). Taken together, the evidence suggests that Big 4 auditors do perform higher quality audits.

Keywords: Big 4 auditor; audit quality; propensity-score matching; audit quality proxies.

JEL Classifications: M41; M42.

Data Availability: All data are publicly available from sources identified in the text.

INTRODUCTION

One of the earliest theories in the audit literature is that Big 4[1] auditors, due to their larger size and better training programs, provide higher audit quality than other auditors. The argument is that larger audit firms have more reputation to lose by sacrificing their independence on any given audit engagement (DeAngelo 1981). In addition, larger audit firms have

John Daniel Eshleman is an Assistant Professor at Oklahoma State University, and Peng Guo is a Ph.D. Student at Louisiana State University.

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[1] We use the term Big 4 to refer to the Big 5 or Big 4 accounting firms.

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Occupational status benefits of studying abroad and the role of occupational specificity – A propensity score matching approach

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ABSTRACT

Occupational status benefits of student mobility remain uncertain, despite increasing interest in the implications of international student mobility for the reproduction of societal inequality. Since mobile young people are a selective group in terms of socio-economic and achievement-oriented factors, we apply propensity score techniques to test whether German higher education graduates who did or did not study abroad differ in occupational status (based on the Socio-Economic Index of Occupational Status) three years after graduation. Analyses are based on multi-cohort representative data of the German population (Working and Learning in a Changing World). Results confirm a positively biased effect of mobility on early career occupational status driven by compositional differences. Subgroup analyses show that even when accounting for this bias, occupational status returns to mobility are positive for those graduating in occupationally unspecific fields of study. There are no returns for those graduating in occupationally specific fields of study. Findings also suggest that the effect of studying abroad is not homogeneous across the study population. Individuals less likely to study abroad are at the same time more likely to reap the occupational benefits from this experience.

1. Introduction and research question

As international exchange schemes and fellowships have gained popularity and as the international education market rapidly grew into a 'multi-billion dollar industry' (Waters, 2006, 180) different disciplines developed a sustained interest into the characteristics, determinants, and consequences of studying abroad during higher education. Up to now, most research has been driven by the question *who* studies abroad (or who doesn't) closely related to discussions about growing horizontal education-based stratification (Lörz et al., 2016; Triventi, 2013). The group of students studying abroad is highly socially selective in terms of the economic, cultural, and social capital of the students' families (Brooks and Waters, 2010; Netz and Finger, 2016; Gerhards and Hans, 2013).

Given that the share of the population reaching secondary and postsecondary levels of education has increased substantially across the educationally expanding Western world, competitions for privileged positions in society have intensified. It is likely that horizontal characteristics of education such as international mobility become more important erecting new dimensions of social stratification and new types of social inequality (Gerber and Cheung, 2008; Reimer and Pollak, 2010, 427). In fact, the benefits of international mobility are often taken for granted. Being mobile possibly strengthens graduates' skills, resources, and competitive advantage on the job market and for this reason may be valued by individuals as well as potential employers (e.g., Opper, 1991).

Based on these observations and assumptions, it is essential to figure out whether studying abroad actually yields returns in terms

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Group 3 papers to be discussed in
Classes 10 and 11 (2021-04-08 and 2021-04-15))

Admon
Becher
Freedberg
Preisser
Retelsdorf
Roze

Emulating a Novel Clinical Trial Using Existing Observational Data

Predicting Results of the PreVent Study

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Abstract

Rationale: "Target trial emulation" has been proposed as an observational method to answer comparative effectiveness questions, but it has rarely been attempted concurrently with a randomized clinical trial (RCT).

Objectives: We tested the hypothesis that blinded analysts applying target trial emulation to existing observational data could predict the results of an RCT.

Methods: PreVent (Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation) was a multicenter RCT examining the effects of positive-pressure ventilation during tracheal intubation on oxygen saturation and severe hypoxemia. Analysts unaware of PreVent's results used patient-level data from three previous trials evaluating airway management interventions to emulate PreVent's eligibility criteria, randomization procedure, and statistical analysis. After PreVent's release, results of this blinded observational analysis were compared with those of the RCT. Difference-in-differences estimates for comparison of treatment effects between the observational analysis and the PreVent trial are reported on the absolute scale.

Results: Using observational data, we were able to emulate PreVent's randomization procedure to produce balanced groups for comparison. The lowest oxygen saturation during intubation was higher in the positive-pressure ventilation group than the no positive-pressure ventilation group in the observational analysis ($n = 360$; mean difference = 1.8%; 95% confidence interval [CI] = −1.0 to 4.6) and in the PreVent trial ($n = 401$; mean difference = 3.9%; 95% CI = 1.4 to 6.4), though the observational analysis could not exclude no difference. Difference-in-differences estimates comparing treatment effects showed reasonable agreement for lowest oxygen saturation between the observational analysis and the PreVent trial (mean difference = −2.1%; 95% CI = −5.9 to 1.7). Positive-pressure ventilation resulted in lower rates of severe hypoxemia in both the observational analysis (risk ratio = 0.60; 95% CI = 0.38 to 0.93) and in the PreVent trial (risk ratio = 0.48; 95% CI = 0.30 to 0.77). The absolute reduction in the incidence of severe hypoxemia with positive-pressure ventilation was similar in the observational analysis (9.4%) and the PreVent trial (12.0%), though the difference between these estimates had wide CIs (mean difference = 2.5%; 95% CI = −8.0 to 13.6%).

Conclusions: Applying target trial emulation methods to existing observational data for the evaluation of a novel intervention produced results similar to those of a randomized trial. These findings support the use of target trial emulation for comparative effectiveness research.

Keywords: clinical trials; intubation; epidemiology; causal inference; target trial emulation

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nature medicine

Brown adipose tissue is associated with cardiometabolic health

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White fat stores excess energy, whereas brown and beige fat are thermogenic and dissipate energy as heat. Thermogenic adipose tissues markedly improve glucose and lipid homeostasis in mouse models, although the extent to which brown adipose tissue (BAT) influences metabolic and cardiovascular disease in humans is unclear[1,2]. Here we retrospectively categorized 134,529 ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography scans from 52,487 patients, by presence or absence of BAT, and used propensity score matching to assemble a study cohort. Scans in the study population were initially conducted for indications related to cancer diagnosis, treatment or surveillance, without previous stimulation. We report that individuals with BAT had lower prevalences of cardiometabolic diseases, and the presence of BAT was independently correlated with lower odds of type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure and hypertension. These findings were supported by improved blood glucose, triglyceride and high-density lipoprotein values. The beneficial effects of BAT were more pronounced in individuals with overweight or obesity, indicating that BAT might play a role in mitigating the deleterious effects of obesity. Taken together, our findings highlight a potential role for BAT in promoting cardiometabolic health.

As early as 2003, reports[3] described increased uptake of the glucose analog ^{18}F-fluorodeoxyglucose (^{18}F-FDG) on positron emission tomography (PET) scans in areas corresponding to supraclavicular fat on computed tomography (CT) images, suggesting the presence of metabolically active BAT in adult humans. In 2009, a series of papers confirmed the presence of active BAT in adults, which correlated with lower body mass index (BMI), decreased age, colder outdoor temperature, female sex and decreased glucose levels[4–6]. Since then, small prospective studies in healthy humans have demonstrated that cold-activated BAT is associated with increased energy expenditure and enhanced disposal of glucose and free fatty acids[7,8]. Although these effects have generated enthusiasm for BAT as a therapeutic target for obesity and associated diseases, these studies have been too small to definitively address whether BAT is a clinically meaningful modulator of metabolic and cardiovascular disease in humans.

To address the relationship of BAT with metabolic and cardiovascular diseases, we reviewed 134,529 ^{18}F-FDG positron emission tomography–computed tomography (PET/CT) reports from 52,487 patients generated between 1 June 2009 and 31 March 2018 at Memorial Sloan Kettering Cancer Center (MSKCC) (Fig. 1a). ^{18}F-FDG PET/CT was conducted for cancer diagnosis, staging, monitoring of treatment response and surveillance, and it is MSKCC protocol to record BAT status in each scan. BAT was reported in 7,923 (5.9%) ^{18}F-FDG PET/CT scans (Fig. 1b and Supplementary Table 1) in 5,070 (9.7%) patients (Fig. 1c and Supplementary Table 2), with reporting consistent from 2009 to 2018 (Extended Data Fig. 1). BAT was more prevalent among women (13.8 versus 4.9%, $P<0.0001$), decreased with age ($r=-0.9850$, $P<0.0001$) and was inversely correlated with ambient temperature ($r=-0.6993$, $P<0.0001$) and BMI ($r=-0.9032$, $P<0.0001$), in accord with earlier, smaller retrospective studies (Fig. 1c–f and Extended Data Fig. 2a,b)[9,10].

To assess accuracy of reporting, all scans conducted in 2016 with reported BAT were manually reviewed (Methods), and BAT activity was measured in six depots (cervical, supraclavicular, axillary, mediastinal, paraspinal and abdominal) (Fig. 1g). Of the 1,139 scans with brown fat identified in 2016, 1,136 (99.7%) showed increased ^{18}F-FDG uptake in regions identified as fat on CT, while 3 (0.3%) were false-positive and reported resolution of previously detected BAT. In total, 1,091 (95.8%) scans met Brown Adipose Reporting Criteria in Imaging STudies (BARCIST 1.0) criteria in terms of ^{18}F-FDG uptake above the recommended threshold of standardized uptake value (SUV) normalized to body mass, $\geq 1.5\,g\,ml^{-1}$ (ref. [11]). As previously reported[12], detected BAT activity was more prevalent in the cervical (81.5%) and supraclavicular depots (87.9%) compared with paraspinal (58.2%), mediastinal (50.1%), axillary (31.4%) and abdominal depots (21.1%) (Fig. 1h). Maximum BAT activity was higher in the supraclavicular depot ($5.4\,g\,ml^{-1}$, interquartile range (IQR) 3.6–8.0) compared with paraspinal ($4.7\,g\,ml^{-1}$, IQR 3.3–6.7, $P<0.0001$), mediastinal ($4.8\,g\,ml^{-1}$, IQR 3.5–7.0, $P=0.0185$) and axillary depots ($4.1\,g\,ml^{-1}$, IQR 3.0–5.6, $P<0.0001$) (Fig. 1i). Lastly, maximum measured BAT activity positively correlated with the number of depots with BAT activity ($r=0.6510$, $P<0.0001$), indicating an association between abundance and activity (Fig. 1j). Patients were then categorized by presence or absence of BAT (BAT^+ and BAT^-, respectively) based on ^{18}F-FDG uptake on PET/CT, and an index scan was assigned as a reference point for data collection (Fig. 1a and described in the Methods). In patients without a BAT signature on any scan, the first ^{18}F-FDG PET/CT scan served

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BRIEF COMMUNICATIONS

Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study

Daniel E. Freedberg,[1] Joseph Conigliaro,[2,3] Timothy C. Wang,[1] Kevin J. Tracey,[4] Michael V. Callahan,[5,6] and Julian A. Abrams,[1] on behalf of the Famotidine Research Group

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See Covering the Cover synopsis on page 803.

Keywords: Coronavirus 2019; SARS-CoV-2; Famotidine; Histamine-2 Receptor Antagonists.

Coronavirus Disease 2019 (COVID-19) caused 2 million cases and more than 150,000 deaths worldwide as of mid-April 2020.[1] Clinical trials are under way to assess the efficacy of a variety of antiviral drugs; however, many of these drugs have toxicities and thus far no drug has been proven to improve outcomes in patients with COVID-19.

Famotidine is a histamine-2 receptor antagonist that suppresses gastric acid production. In vitro, famotidine inhibits human immunodeficiency virus replication.[2] Recently, Wu et al.[3] used computational methods to predict structures of proteins encoded by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome and identified famotidine as one of the drugs most likely to inhibit the 3-chymotrypsin-like protease ($3CL^{pro}$), which processes proteins essential for viral replication.[4] We hypothesized that famotidine would be associated with improved clinical outcomes among hospitalized patients with COVID-19. To explore this, we performed a retrospective cohort study at a single academic center located at the epicenter of the COVID-19 pandemic in the United States.

Methods

Complete methods are available in the Supplementary Materials. In brief, adults were eligible for the study if they were admitted to our institution from February 25, 2020, to April 13, 2020, and tested positive for SARS-CoV-2 within no more than 72 hours following admission. Patients were excluded if they died or were intubated within 48 hours following hospital admission. The primary exposure was use of famotidine (any dose, form of administration, or duration), classified as present if famotidine was received within 24 hours of hospital admission and otherwise as absent. The primary outcome was a composite of death or endotracheal intubation from hospital day 2 to day 30 (intubation-free survival). This follow-up period avoided immortal time bias because the exposure was classified based on the 24-hour period after hospitalization and the at-risk period began on hospital day 2. Cox proportional hazards modeling was performed on the full cohort, and a matched subset was examined with propensity scoring matching to balance baseline characteristics based on use of famotidine.

Results

Population and Use of Famotidine

A total of 1620 patients met criteria for analysis, including 84 patients (5.1%) who received famotidine within 24 hours of hospital admission. Home use of famotidine was documented on admission medication reconciliation in 15% of those who used famotidine while hospitalized compared with 1% of those who did not ($P < .01$). Twenty-eight percent of all famotidine doses were intravenous; 47% were 20 mg, 35% were 40 mg, and 17% were 10 mg. Famotidine users received a median 5.8 days of drug for a total median dose of 136 mg (63–233 mg). There were minimal differences comparing patients who used famotidine with those who did not, and balance between the groups was further improved after propensity score matching (Supplementary Table 1).

Death or Intubation

A total of 142 (8.8%) patients were intubated and 238 (15%) died; 340 (21%) patients met the composite study outcome. In crude analysis, use of famotidine was significantly associated with reduced risk for the composite outcome of death or intubation (Figure 1*A*, log-rank $P < .01$). This association was driven primarily by the relationship between famotidine and death (Figure 1*B*, log-rank

Abbreviations used in this paper: **CI, confidence interval; COVID-19, Coronavirus Disease 2019; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.**

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Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients with D'Amico Intermediate and High Risk Prostate Cancer Treated with Radical Prostatectomy: A Multi-Institutional Study

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Abbreviations and Acronyms

BCR = biochemical recurrence
CSM = cancer specific mortality
ePLND = extended PLND
LNI = lymph node invasion
PCa = prostate cancer
PLND = pelvic lymph node dissection
PSA = prostate specific antigen
RP = radical prostatectomy

Purpose: Pelvic lymph node dissection represents the gold standard of lymph node staging in patients with prostate cancer. We sought to assess the effect of extended pelvic lymph node dissection on oncologic outcomes in patients with characteristics of D'Amico intermediate or high risk prostate cancer treated with radical prostatectomy.

Materials and Methods: In a multi-institutional database of 4 centers we identified 9,742 patients who underwent radical prostatectomy from 2000 to 2017 with or without pelvic lymph node dissection. Only patients with a greater than 5% probability of lymph node invasion according to the Briganti nomogram were included in study. We performed 2:1 propensity score matching to account for potential differences between the 2 cohorts. Cox regression models were used to test the effect of pelvic lymph node dissection on biochemical recurrence, metastasis and cancer specific mortality.

Results: Overall 707 patients (7.3%) did not undergo pelvic lymph node dissection, of whom 520 and 187 harbored D'Amico intermediate and high risk characteristics, respectively. A median of 14 lymph nodes (IQR 8–21) were removed in the pelvic lymph node dissection cohort and 1,714 of these cases (19.0%) harbored lymph node metastasis. After propensity score matching the biochemical recurrence-free, metastasis-free and cancer specific mortality-free survival rates were 60.4% vs 65.6% (p=0.07), 87.0% vs 90.0% (p=0.06) and 95.2% vs 96.4% (p=0.2) for pelvic lymph node dissection vs no pelvic lymph node dissection 120 months after radical prostatectomy. Multivariable Cox regression models adjusted for postoperative and preoperative tumor characteristics revealed that pelvic lymph node dissection

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Reading development in a tracked school system: A longitudinal study over 3 years using propensity score matching

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Background. Assigning students to different school tracks on the basis of their achievement levels is a widely used strategy that aims at giving students the best possible learning opportunity. There is, however, a growing body of literature that questions such positive effects of tracking.

Aims. This study compared the developmental trajectories of reading comprehension and decoding speed between students at academic track schools that typically prepare students for university entrance and students at non-academic track schools that usually prepare students for vocational education.

Sample. In a longitudinal design with three occasions of data collection, the authors drew on a sample of $N = 1{,}508$ 5th graders (age at T1 about 11 years, age at T3 about 14 years) from 60 schools in Germany. The academic track sample comprised $n = 568$ students; the non-academic track sample comprised $n = 940$ students.

Method. Achievement measures were obtained by standardized tests of reading comprehension and decoding speed. Students at the different tracks were closely matched using propensity scores. To compare students' growth trajectories between the different school tracks, we applied multi-group latent growth curve models.

Results. Comparable results were recorded for the complete (unmatched) sample and for the matched pairs. In all cases, students at the different tracks displayed a similar growth in reading comprehension, whereas larger growth rates for students at academic track schools were recorded for decoding speed.

Conclusions. Our findings contribute to an increasing body of literature suggesting that tracking might have undesired side effects.

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See corresponding editorial on page 713.

Nutritional strategies and gut microbiota composition as risk factors for necrotizing enterocolitis in very-preterm infants

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ABSTRACT

Background: The pathophysiology of necrotizing enterocolitis (NEC) remains poorly understood.

Objective: We assessed the relation between feeding strategies, intestinal microbiota composition, and the development of NEC.

Design: We performed a prospective nationwide population-based study, EPIPAGE 2 (Etude Epidémiologique sur les Petits Ages Gestationnels), including preterm infants born at <32 wk of gestation in France in 2011. From individual characteristics observed during the first week of life, we calculated a propensity score for the risk of NEC (Bell's stage 2 or 3) after day 7 of life. We analyzed the relation between neonatal intensive care unit (NICU) strategies concerning the rate of progression of enteral feeding, the direct-breastfeeding policy, and the onset of NEC using general linear mixed models to account for clustering by the NICU. An ancillary propensity-matched case-control study, EPIFLORE (Etude Epidémiologique de la flore), in 20 of the 64 NICUs, analyzed the intestinal microbiota by culture and 16S ribosomal RNA gene sequencing.

Results: Among the 3161 enrolled preterm infants, 106 (3.4%; 95% CI: 2.8%, 4.0%) developed NEC. Individual characteristics were significantly associated with NEC. Slower and intermediate rates of progression of enteral feeding strategies were associated with a higher risk of NEC, with an adjusted OR of 2.3 (95% CI: 1.2, 4.5; $P = 0.01$) and 2.0 (95% CI: 1.1, 3.5; $P = 0.02$), respectively. Less favorable and intermediate direct-breastfeeding policies were associated with higher NEC risk as well, with an adjusted OR of 2.5 (95% CI: 1.1, 5.8; $P = 0.03$) and 2.3 (95% CI: 1.1, 4.8; $P = 0.02$), respectively. Microbiota analysis performed in 16 cases and 78 controls showed an association between *Clostridium neonatale* and *Staphylococcus aureus* with NEC ($P = 0.001$ and $P = 0.002$).

Conclusions: A slow rate of progression of enteral feeding and a less favorable direct-breastfeeding policy are associated with an increased risk of developing NEC. For a given level of risk assessed by propensity score, colonization by *C. neonatale* and/or *S. aureus* is significantly associated with NEC. This trial (EPIFLORE study) was registered at clinicaltrials.gov as NCT01127698. *Am J Clin Nutr* 2017;106:821–30.

Keywords: breastfeeding, clostridia, necrotizing enterocolitis, preterm infant, speed of increasing enteral nutrition

INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the most dreaded diseases in neonatal intensive care units (NICUs) (1, 2). The

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Supplemental Figures 1–4, Supplemental Methods, and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Abbreviations used: EPIFLORE, Etude Epidémiologique de la flore; EPIPAGE 2, Etude Epidémiologique sur les Petits Ages Gestationnels; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; rRNA, ribosomal RNA.

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