the development of early career scientists. Dedicated mentors working in teams to support the development of our emerging scientists are essential to their success. Supporting an interdisciplinary environment with team science and mentorship will require that we realign our culture, values, infrastructure, and investments to reward and promote collaborative accomplishments.

Second, we need to invent ways to revitalize chance interactions and support social networking. Virtual scientific conferences should freely include mentoring and networking sessions, and after a period of time, these conferences should be made universally accessible. However, we need to advance novel approaches to stimulate spontaneity in our professional lives.

Third, we need to recognize that additional responsibilities at home represent key drivers that not only limit career development but force some of our colleagues to leave medicine and science. Programs addressing childcare, home schooling, cleaning services, and eldercare are needed to restore balance to home and work. We also need to think more creatively about flexible work expectations and more broadly about work environments and support a culture in which both men and women are accepted as caregivers.

Fourth, we need to recognize that these additional responsibilities and competing priorities, along with isolation and loneliness, take an emotional toll. Consequently, although wellness programs are essential, work environments should foster trust, inclusion and equity, and career development and provide dedicated mentorship (1).

Fifth, funding agencies are critical to reinvestment in our scientists. Although extending deadlines for grant submission, relaxing recruitment milestones, and expanding the scope of no-cost extensions have proved helpful, funding agencies should also consider developing programs to give scientists back the time lost to COVID-19. Emerging scientists would benefit from fully funded extensions of mentored research and early career development awards. The NIH can establish programs, similar in impact to the Doctor Draft for the Korean and Vietnam Wars, that would reinvigorate the pool of physician-scientists. Expanded support for trainees and emerging scientists should be considered, focusing on transition points in career development and programs that stimulate collaboration between M.D. and Ph.D. scientists (9).

Sixth, AMCs and philanthropic foundations should recognize that their financial reserves were established to provide support in times of need. Investments should be focused on our scientists who are torn between their careers and their families, and those who need to make up for time lost to the pandemic. Start-up packages should be extended, investments should be made in infrastructure to stimulate programmatic research, and early career scientists should be provided additional time to reach their scientific goals.

Finally, there is the larger problem of how science is valued by our nation, which, despite the current economic travails brought about by the pandemic, is wealthy. Congress must now face up to the sad lessons learned from the ways science has been pushed aside in the pandemic by political leaders and substantially increase the federal research budget. It is time to go big.

Concluding Remarks

To sustain our scientific pipeline and ensure the future of academic medicine, there is an urgent need for funding agencies, schools of medicine, AMCs, and philanthropic foundations to address the challenges the pandemic has imposed with bold approaches that will require realignment of our culture, values, infrastructure, and investments. To do nothing, or to continue the status quo, is not an option. ■

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Marisha Burden, M.D.
Sonia C. Flores, Ph.D.
David A. Schwartz, M.D.*
University of Colorado
Aurora, Colorado

*Corresponding author (e-mail: david.schwartz@cuanschutz.edu).

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ACE2 Elevation in Severe COVID-19

To the Editor:

ACE2 (angiotensin-converting enzyme 2) serves as the entry receptor for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease (COVID-19). ACE2 is also the key enzyme of the *alternative* renin–angiotensin

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system (RAS) and counterbalances angiotensin II activity by enzymatically converting angiotensin II to angiotensin 1–7. Anchored in the membrane of type II alveolar and lung epithelial cells, ACE2 can be cleaved by the metalloproteinase ADAM17 (1).

In an earlier study, infection of mice with SARS-CoV-1, the coronavirus causing the 2002–2004 severe acute respiratory syndrome outbreak, resulted in lung injury, which appeared to be mediated by ACE2 downregulation and impaired degradation of angiotensin II (2). In line, the genetic deletion of ACE2 in mice led to a more severe disease course in an influenza model (3). However, gene expression data from BAL fluid cells suggest that, in humans, ACE2 becomes upregulated by IFN during SARS-CoV-2 infection (4). Moreover, significantly greater numbers of ACE2-positive cells were counted in the lungs from patients who died of COVID-19 or influenza compared with uninfected control subjects (5). Hypothesizing that ACE2 may play an essential role in the human response to viral lung injury, we aimed at assessing plasma ACE2 in patients with COVID-19 of variable severity over the time course of their disease in comparison with a retrospective cohort of patients with influenza.

Methods

We measured enzymatically active plasma ACE2 concentration (subsequently referred to as "ACE2") and key RAS metabolites in 532 blood samples obtained from 126 patients with SARS-CoV-2 infection admitted to the primary COVID-19 care facility in the metropolitan area of Vienna (Klinik Favoriten) between March 15 and June 30, 2020. The study was approved by the Ethics Committee of the Medical University of Vienna (EK#1315/2020). Severity of disease was graded by the maximum requirement for respiratory support during hospitalization as severe (requiring invasive, mechanical ventilation at least once during the disease course) versus nonsevere (ranging from asymptomatic [patients who were hospitalized for non–SARS-CoV-2–related disease on top of SARS-CoV-2 infection] to noninvasive ventilation). As a comparator group, we included 27 patients who had been critically ill with influenza pneumonia, all requiring invasive, mechanical ventilation (years 2015–2019), and measured ACE2 and RAS metabolites from their previously stored serum samples. The equilibrium concentrations of the RAS metabolites angiotensin II and angiotensin 1–7 were determined by liquid chromatography–tandem mass spectrometry (Attoquant Diagnostics), as previously described (6). ACE2 was quantified using a natural substrate conversion assay (by quantifying angiotensin 1–7 formation from angiotensin II with commercially available recombinant human ACE2 as calibrator) (7). The starting point for all analyses was the day of hospitalization or transfer to our dedicated COVID-19 care facility after testing positive for SARS-CoV-2 at another hospital (Day 0). For statistical between-group comparisons of baseline characteristics and clinical variables, we used Student's t test, χ^2, and Fisher's exact tests when appropriate. Laboratory values, ACE2 and RAS metabolite concentrations were compared between groups and by disease severity using Mann-Whitney U test. Multiple measurements per individual were averaged over given time intervals (all time points, Days 0–3 [early], and Days 9–11 [late]). A mixed-effects model was used to predict ACE2, as further described below.

Results

Baseline characteristics, covariables, and clinical outcomes of the study patients (patients with COVID-19 [stratified by disease severity] and patients with influenza) are provided in Table 1. Antivirals and immunomodulatory medication differed by COVID-19 severity. As shown in Figure 1, ACE2 in patients with COVID-19 increased over time, especially in severe patients, in whom ACE2 reached a peak of 15.1 ng/ml during the late time interval (Days 9–11), compared with 3.2 ng/ml in nonsevere patients ($P < 0.001$). ACE2 during the early time interval (Days 0–3) was 2.1 ng/ml in patients with severe COVID-19 and 1.3 ng/ml in patients with nonsevere COVID-19 ($P = 0.078$).

On the RAS metabolite level, we analyzed substrate (angiotensin II) and product (angiotensin 1–7) of ACE2. Early angiotensin II concentrations were significantly higher in patients with severe versus nonsevere COVID-19 (165.7 vs. 47.7 pmol/L; $P < 0.01$) but subsequently decreased in both groups. Simultaneously, angiotensin 1–7 concentrations increased from 10.8 pmol/L (early) to 49.8 pmol/L (late) in patients with severe COVID-19 (Table 1). The angiotensin-1–7–to–angiotensin-II ratio increased from 7% (early) to 31% (late) in patients with severe COVID-19, suggesting an increase in the formation of angiotensin 1–7 from angiotensin II. In patients with nonsevere COVID-19, we observed no statistically significant increase in alternative RAS metabolites.

ACE2 in patients with influenza was significantly lower compared with patients with severe COVID-19 but showed a similar time-dependent pattern, with higher values measured in samples obtained at later time points after intubation (2.4 ng/ml and 5.3 ng/ml for the Day 0–3 time interval and after Day 5, respectively; $P < 0.05$).

We used a mixed-effects model to identify factors associated with ACE2 (on the log scale) in COVID-19 (overall goodness of fit: $r^2 = 0.789$). To account for the nonlinear time trends as well as the distinct behaviors observed in Figure 1, we introduced a term for severity of disease and linear and quadratic terms for time (i.e., days since hospitalization) as well as interaction terms for the time-dependent variables and severity of disease. In a parsimonious model, we further included patient sex and history of diabetes and hypertension on the basis of significant model improvements tested via likelihood ratio tests. Additional covariables that were tested but not selected for the final model were RAS-inhibitor comedication at time of hospitalization, treatment with corticosteroids, history of chronic obstructive pulmonary disease, and age (they did not improve the overall performance of the model).

Factors significantly associated with ACE2 trajectories were COVID-19 severity, days after hospitalization (linear and quadratic), and the interaction terms. The significant interactions supported the observation of increasing ACE2 in patients with severe COVID-19, with a subsequent decline, realized in the model via a linear positive effect for time (on antilog scale: factor, 1.42; 95% confidence interval [CI], 1.32–1.53 per day) and a nonlinear negative effect for square of time (factor, 0.99; 95% CI, 0.98–0.99). Additional factors that were associated with higher ACE2 were male sex (factor, 1.57; 95% CI, 1.18–2.09) and history of diabetes (factor, 1.42; 95% CI, 1.05–1.91). Among key laboratory parameters (IL-6, C-reactive protein, serum creatinine, and D-dimer), only IL-6 concentrations were significantly associated with ACE2 concentration in the mixed-effects model.

Regarding the influence of immunomodulatory therapy and antivirals, median ACE2 concentrations in patients treated with corticosteroids (compared with no corticosteroids) were 9.9 (interquartile range [IQR], 6.9–17.4) ng/ml and 11.3 (IQR, 6.4–18.1) ng/ml, respectively ($P = 0.969$). Median ACE2 concentrations in patients receiving antiinflammatory treatment with tocilizumab (compared with no tocilizumab) were 12.6 (IQR, 6.0–31.8) ng/ml

Table 1. Demographics, Clinical Characteristics, and RAS Profiles of Patients with COVID-19 and Influenza

Baseline Characteristics, Medication, and Outcome					
	COVID-19 (*n* = 126)			*P* Value	
	Nonsevere COVID-19 (*n* = 94)	Severe COVID-19 (*n* = 32)	Comparator: Influenza (*n* = 27)	Nonsevere vs. Severe COVID-19	Severe COVID-19 vs. Influenza
Demographics					
Age, yr	59 (47–77)	68 (53–74)	58 (49–64)	0.207	**<0.05**
Sex, F	34 (36.2)	7 (21.9)	11 (40.7)	0.136	0.067
BMI	27.2 (24.5–30.6)	25.7 (20.5–42.5)	n.a.	0.740	n.a.
Comorbidities					
Diabetes	28 (30.1)	11 (35.5)	3 (13.6)	0.577	0.075
Hypertension	47 (50.5)	20 (64.5)	2 (9.1)	0.176	**<0.001**
COPD	7 (7.5)	6 (19.4)	3 (13.6)	0.063	0.585
RAS inhibitor comedication					
ACEi	16 (17.2)	2 (6.5)	2 (9.1)	0.141	0.720
ARB	14 (15.1)	8 (25.8)	2 (9.1)	0.175	0.125
Antiviral medication					
Hydroxychloroquine	8 (8.5)	6 (18.8)	n.a.	0.111	n.a.
Lopinavir/ritonavir	19 (20.2)	11 (34.4)	n.a.	0.104	n.a.
Remdesivir	4 (4.3)	10 (31.2)	n.a.	**<0.001**	n.a.
Convalescent plasma	2 (2.1)	4 (12.5)	n.a.	**<0.05**	n.a.
Camostat	25 (26.6)	0 (0.0)	n.a.	**<0.001**	n.a.
Immunomodulatory medication					
Tocilizumab	1 (1.1)	6 (18.8)	n.a.	**<0.001**	n.a.
Steroids	8 (8.6)	11 (34.4)	n.a.	**<0.001**	n.a.
Laboratory values					
Baseline CRP,* mg/L	46.7 (19.5–82.7)	120.90 (65.0–283.7)	69.8 (32.1–226.1)	**<0.001**	0.188
Maximum CRP,† mg/L	58.9 (19.9–112.5)	188.70 (102 –324.3)	314.0 (211.9–338.2)	**<0.001**	**<0.05**
Baseline D-dimer,* mg/L	0.96 (0.62–1.97)	1.81 (0.82–4.27)	n.a.	**<0.05**	n.a.
Maximum D-dimer,† mg/L	1.63 (0.68–3.00)	6.45 (2.67–15.55)	n.a.	**<0.001**	n.a.
Baseline creatinine,* mg/dl	0.86 (0.71–1.12)	1.20 (0.78–1.50)	1.29 (0.91–1.67)	**<0.05**	0.316
Maximum creatinine,† mg/dl	0.94 (0.76–1.17)	1.42 (0.93–2.24)	2.13 (1.47–3.46)	**<0.001**	**<0.05**
Baseline IL-6,* pg/ml	25.1 (9.8–50.2)	152.00 (68.8–369.3)	n.a.	**<0.001**	n.a.
Maximum IL-6,† pg/ml	25.8 (9.8–56.6)	368.50 (138.5–1,448.5)	n.a.	**<0.001**	n.a.
Severity of disease					
SOFA score	n.a.	9 (8–11)	9 (8–11)	n.a.	0.551
Outcome					
Length of hospital stay, d	16 (10–26.5)	31 (28–45)	41 (25–66)	**<0.001**	**<0.05**
Death	4 (4.3)	11 (34.4)	8 (29.6)	**<0.001**	0.581

(Continued)

Table 1. (*Continued*)

	RAS Profiles									
	COVID-19					*P* Value				
	Nonsevere COVID-19		Severe COVID-19							
	Days 0–3 (Early)	Days 9–11 (Late)	Days 0–3 (Early)	Days 9–11 (Late)	Comparator: Influenza	Nonsevere: Early vs. Late COVID-19	Severe: Early vs. Late COVID-19	Early: Severe vs. Nonsevere COVID-19	Late: Severe vs. Nonsevere COVID-19	Severe COVID-19 vs. Influenza
ACE2, ng/ml	1.3 (1.0–2.4)	3.2 (1.8–4.7)	2.1 (1.3–3.0)	15.1 (9.8–31.8)	3.5 (2.3–6.6)	**<0.001**	**<0.001**	0.078	**<0.001**	**<0.001**
Angiotensin II, pmol/L	47.7 (16.3–131.7)	32.9 (9.3–78.2)	165.7 (61.2–680.6)	95.7 (37.5–250.0)	114.4 (27.0–435.2)	0.105	0.259	**<0.01**	**<0.01**	0.378
Angiotensin 1–7, pmol/L	1.5 (1.5–5.0)	1.5 (1.5–3.7)	10.8 (5.1–50.7)	49.8 (14.6–132.0)	21.0 (59–92.1)	0.681	0.103	**<0.001**	**<0.001**	0.551
Angiotensin-1–7–to–angiotensin-II ratio	0.05 (0.03–0.15)	0.10 (0.04–0.22)	0.07 (0.04–0.13)	0.31 (0.21–0.72)	0.17 (0.10–0.47)	0.129	**<0.001**	0.545	**<0.001**	0.671

Definition of abbreviations: ACE2 = angiotensin-converting enzyme 2; ACEi = ACE inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CRP=C-reactive protein; n.a. = not applicable; RAS = renin–angiotensin system; SOFA = Sequential Organ Failure Assessment. Continuous variables are presented as medians (quartile 1–quartile 3); binary variables are presented as *n* (%). Baseline characteristics and medication were compared using Student's *t*, χ^2, and Fisher's exact tests, when appropriate, whereas laboratory data and ACE2 and RAS metabolite concentrations were compared by Mann-Whitney *U* tests. RAS metabolites and ACE2 in influenza samples were compared with the average value across all available time points in patients with severe COVID-19. The influenza cohort was assembled retrospectively using serum samples obtained for clinical routine and stored at the Department of Virology of the Medical University of Vienna. Longitudinal sampling in individuals with influenza was therefore not available for RAS profiling, as samples were obtained at different time points during the course of their disease (ranging from Day 0 to Day 21 after hospitalization). Significant *P* values are given in bold.

*First value.

†Highest value. Regarding the comparisons between patients with influenza and those with severe COVID-19, note that these comparisons were done between single measurements per patient (in patients with influenza) and averages across all time points per patient (in patients with severe COVID-19).

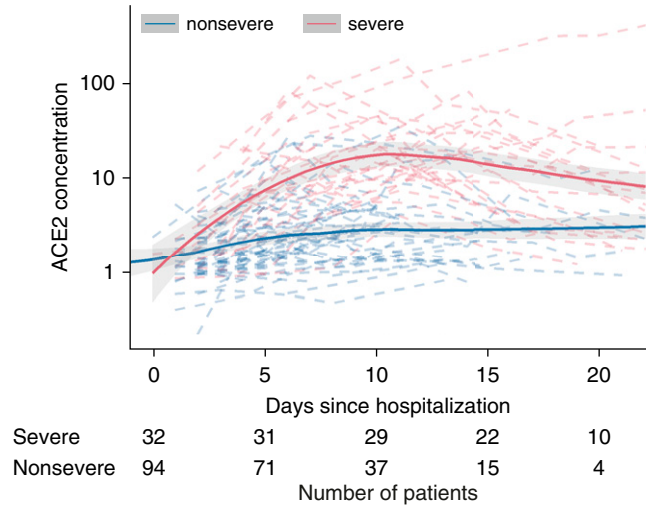

Figure 1. Systemic ACE2 (angiotensin-converting enzyme 2) concentration in coronavirus disease (COVID-19) over time stratified by severity of disease. ACE2 increased in patients with severe COVID-19, peaking during the Day 9–Day 11 time interval after hospitalization. On Day 10 of follow-up, 29 of all 32 patients with severe COVID-19 were still alive, and the respective renin–angiotensin system (RAS) data were included in RAS profile analysis, reducing a potential bias introduced by the overall high mortality rate in severe COVID-19 that could impact ACE2 and RAS metabolite trajectories. Continuous lines represent local regression curves with 95% local confidence intervals, whereas dashed lines represent individual patient-level data, with blue and red lines for nonsevere and severe COVID-19, respectively. Numbers at the bottom indicate number of patients available for analysis at each time point. ACE2 concentration is reported in ng/ml.

and 10.6 (IQR, 7.1–17.2) ng/ml, respectively ($P = 0.760$). Antiviral treatment did not have a statistically significant impact on ACE2 concentrations or RAS metabolites (data not shown).

Discussion

In the present study, the main finding was a sevenfold increase in ACE2 in patients with severe COVID-19 from early to late time periods during their disease course. ACE2 was associated with IL-6, supporting a link with inflammation. Immunomodulatory treatment with corticosteroids or tocilizumab, however, did not have an impact on ACE2 concentrations.

The observed increase in ACE2 in severe COVID-19 was accompanied by an increase in the alternative RAS metabolite angiotensin 1–7 and an increase in the angiotensin-1–7–to–angiotensin-II ratio, indicating a shift toward the potentially protective alternative RAS. Angiotensin 1–7 signaling via the MAS receptor promotes antifibrosis and antagonizes angiotensin II–mediated effects such as vasoconstriction, fibrosis, and thrombogenesis (2).

Higher ACE2 concentrations later during the course of disease in the influenza cohort as well as previously published data on elevated ACE2 in patients with acute respiratory distress syndrome (8) point to a potentially uniform response in those with (virus-induced) severe lung injury. However, ACE2 in patients with severe COVID-19 was significantly higher compared with patients with influenza with similar disease severity based on the Sequential Organ Failure Assessment score (Table 1) and requirement for mechanical ventilation in both groups. Different intubation strategies may hamper direct comparability. Longitudinal analyses of changes in RAS enzyme activity and metabolites are therefore required to draw more definite conclusions on RAS (dys)regulation in other critically ill patients. Currently, systemic application of human recombinant soluble ACE2 is tested as a treatment strategy in severe COVID-19 (9).

Immunomodulatory treatment, antivirals, or RAS medication at the time of hospitalization did not have a statistically significant impact on ACE2, but numbers of patients in respective groups were small. Additional data are necessary to determine how different treatment strategies may impact ACE2 concentrations in COVID-19. A pronounced increase of ACE2 in severe COVID-19 was nevertheless observed across all groups. Systemic ACE2 in severe COVID-19 increased to concentrations that could directly affect systemic angiotensin concentrations, balancing the RAS toward the alternative axis. The observed increase in plasma ACE2 activity in severe COVID-19 may therefore reflect an inflammation-driven, pathophysiological mechanism aimed at counterbalancing an excess of angiotensin II. ■

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Roman Reindl-Schwaighofer, M.D., Ph.D.
Sebastian Hödlmoser, M.Sc.
Farsad Eskandary, M.D., Ph.D.
Medical University of Vienna
Vienna, Austria

Marko Poglitsch, Ph.D.
Attoquant Diagnostics
Vienna, Austria

Diana Bonderman, M.D., Ph.D.
Klinik Favoriten
Vienna, Austria

Robert Strassl, M.D.
Judith H. Aberle, M.D.
Rainer Oberbauer, M.D., Ph.D.
Medical University of Vienna
Vienna, Austria

Alexander Zoufaly, M.D.*
Klinik Favoriten
Vienna, Austria

Manfred Hecking, M.D., Ph.D.*‡
Medical University of Vienna
Vienna, Austria

ORCID ID: 0000-0002-8047-2395 (M.H.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: manfred.hecking@meduniwien.ac.at).

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Trends in Chronic Obstructive Pulmonary Disease Prevalence, Incidence, and Health Services Use in Younger Adults in Ontario, Canada, 2006–2016

To the Editor:

Chronic obstructive pulmonary disease (COPD), a chronic disease that results in progressive loss of lung function, is typically diagnosed in those >65 years of age (1); however, it can be diagnosed at a much younger age. Examining COPD in younger adults—who are often earlier in the natural history of the disease and have milder airflow limitation—may yield new opportunities to introduce behavioral interventions and targeted therapy to slow disease progression (2).

Younger adults with COPD remain poorly described. The limited amount of research characterizing them has primarily been drawn from unrepresentative samples where generalizability may be limited. Furthermore, relevant population-based studies conducted in younger cohorts have not used an appropriate comparison group of older adults (3, 4). We investigated trends in physician-diagnosed COPD incidence, prevalence, and health services use in younger adults and compared them with those in middle-aged and older adults in the province of Ontario, Canada, from fiscal years 2006/2007 to 2016/2017.

Methods

We conducted a population-based study of all Ontario adults (35 yr of age and older) with and without physician-diagnosed COPD to examine and compare COPD trends in people of different ages. Outcomes, including annual COPD prevalence and incidence as well as annual rates of COPD-specific hospitalizations, emergency department (ED) visits (that did not result in a hospitalization), and physician office visits, were calculated between April 1, 2006, and March 31, 2017. Data were from several health administrative databases that were linked using unique identifiers and analyzed at ICES. These data have been described in detail elsewhere (1, 5). ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. People with physician-diagnosed COPD were identified using a validated definition with 57.5% sensitivity and 95.4% specificity (6, 7).

Annual crude and standardized physician-diagnosed COPD prevalence and incidence were calculated in three different age groups: *1*) younger adults 35–54 years old, *2*) middle-aged adults 55–64 years old, and *3*) older adults 65 years and older. Age-specific hospitalization, ED visit, and physician office visit rates were calculated in persons with COPD. Prevalence and incidence were age- and sex-standardized to the general 2016 Ontario population and health service use rates standardized to the 2016 COPD population. Comparisons of longitudinal trends between groups were quantified using the percent change from 2006 to 2016 as well as a generalized linear model with binomial distributions and logit link function for each outcome.

Ethics approval was obtained from Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada. Analysis was done using SAS Enterprise Guide 7.1 (SAS Institute Inc.).

Results

In 2016, crude prevalence of physician-diagnosed COPD was 5.1% in younger adults (50.6 per 1,000) aged 35–55 compared with 13.3% and 21.7% in middle-aged and older adults, respectively. Crude COPD incidence rates in 2016 were 4.8, 8.7, and 13.7 per 1,000 in younger, middle-aged, and older adults, respectively. Standardized COPD prevalence remained stable in the older age group but increased in younger (+13.3%) and middle-aged adults (+17.3%). Unlike the other groups, there was an initial increase in standardized incidence in the younger age group until 2009 and then a decrease (Figure 1).

Standardized rates of COPD-specific hospitalizations, ED visits, and physician visits in younger adults with COPD in 2016 were 7.8, 12.2, and 78.8 per 1,000, respectively. Health services use rates were consistently lowest in younger adults relative to others. There were subtle differences in trends over time between the groups (Figure 2). In the middle-aged and older age groups, hospitalizations and physician office visits for COPD decreased ($P < 0.001$) over a 10-year period from 2006 to 2016; however, this trend was not observed in the younger group ($P < 0.001$). Conversely, ED visits for COPD increased in all three groups

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