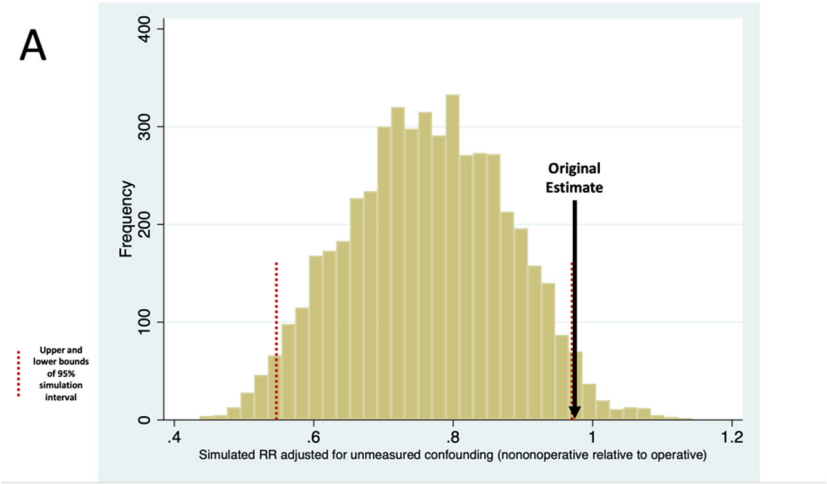
Supplemental Online Content

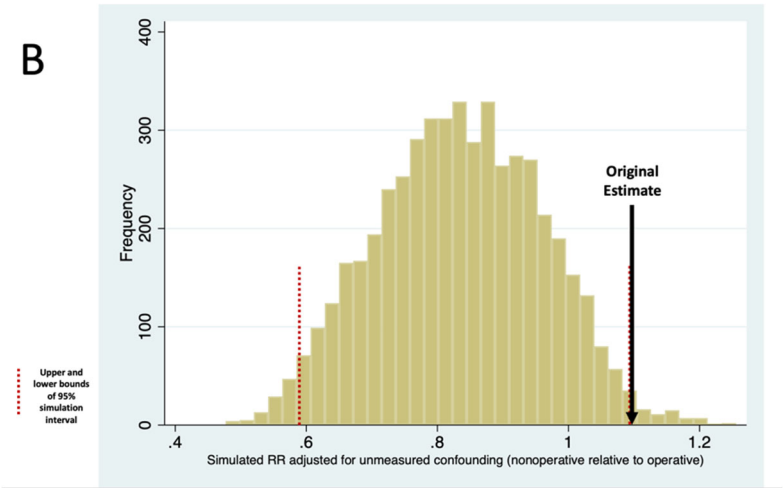
Meier J, Stevens A, Bhat A, Berger M, Balentine C. Outcomes of nonoperative vs operative management of acute appendicitis in older adults in the US. *JAMA Surg*. Published online April 5, 2023. doi:10.1001/jamasurg.2023.0284

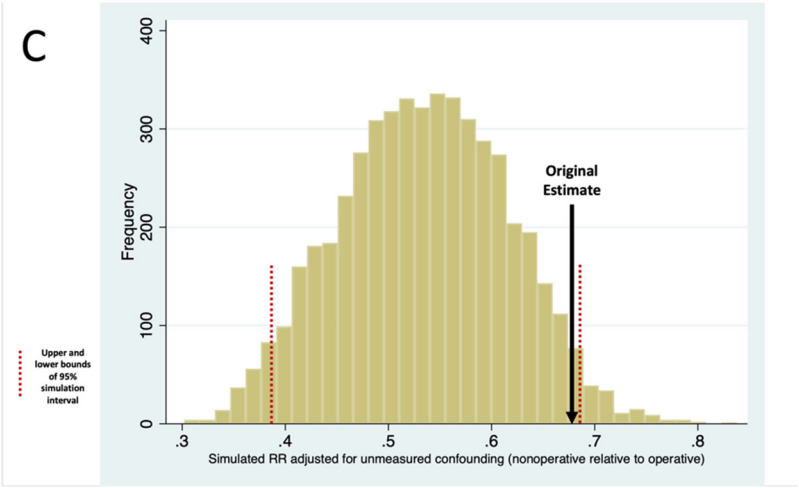
This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. a probabilistic sensitivity analysis - nonoperative management of acute appendicitis and complications

In order to verify our results, we conducted a probabilistic sensitivity analysis to determine the effect that an unmeasured confounding variable would have on the association between nonoperative management of acute appendicitis and complications for (A) all patients, (B) those <65 years, and (C) those 65 years and older.

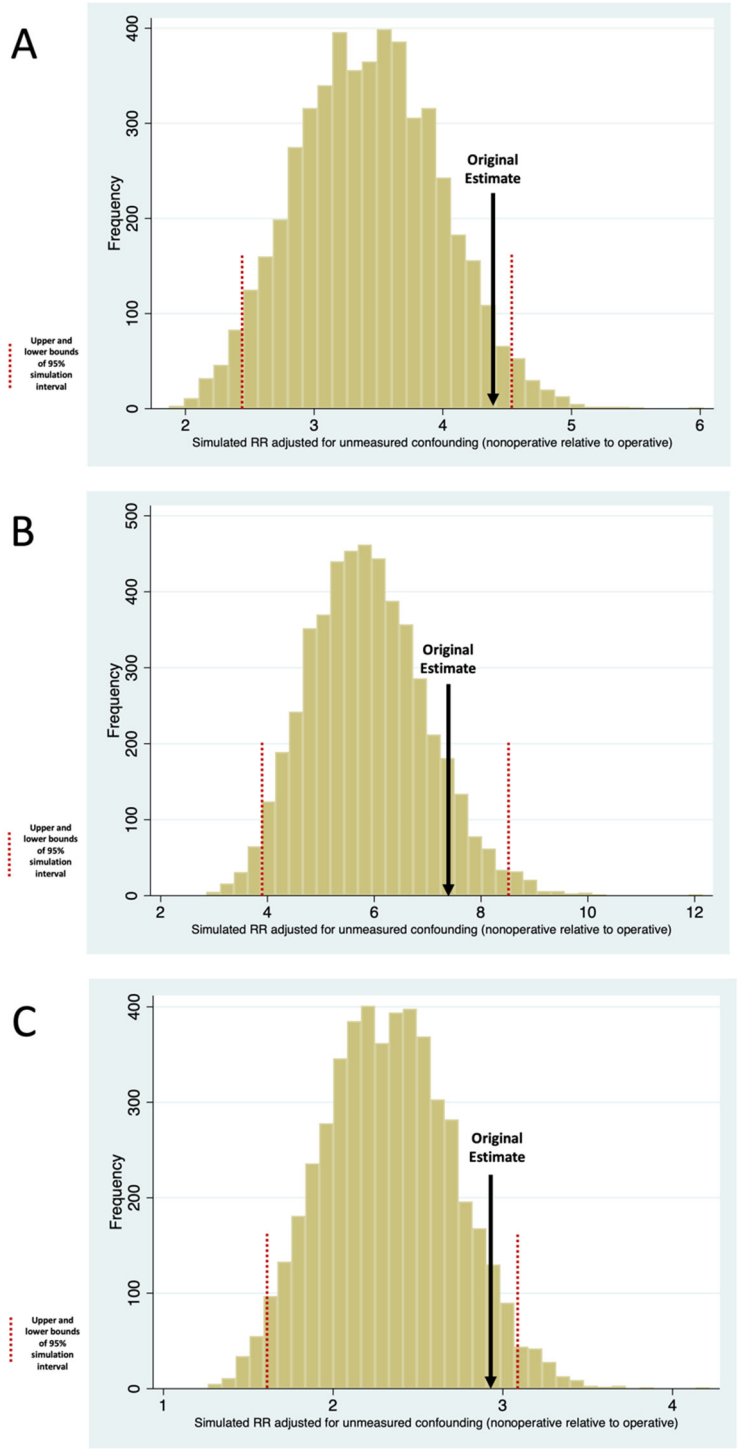






eFigure 2. a probabilistic sensitivity analysis - nonoperative management of acute appendicitis and mortality

We conducted a probabilistic sensitivity analysis to determine the effect that an unmeasured confounding variable would have on the association between nonoperative management of acute appendicitis and mortality for (A) all patients, (B) those <65 years, and (C) those 65 years and older.



eMethods. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	A retrospective cohort study comparing outcomes of nonoperative versus operative management of acute appendicitis in older adults
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	**Design:** Retrospective cohort study of the National Inpatient Sample from 2004-2017 **Setting:** National database study of US hospital admissions **Participants:** We included 474,845 patients admitted with acute, uncomplicated appendicitis treated nonoperatively (n=43,846) or with appendectomy (n=430,999) **Exposure:** Nonoperative versus operative management. **Main Outcomes and Measures:** The primary outcome was incidence of posttreatment complications. Secondary outcomes included mortality, length of stay, and inpatient costs. Differences were estimated using inverse probability weighting of the propensity score with sensitivity analysis to quantify effects of unmeasured confounding. **Results:** The median age was 39 years (IQR 27-54). In patients 65+ years old, nonoperative management was associated with a 3.72% decreased risk of complications (95% CI -2.99%- -4.46%), but a 1.8% (95% CI 1.5%-2.2%) increase in mortality along with increased length of hospitalization and costs. **Conclusions and Relevance:** Nonoperative management was associated with reduced complications in older but not younger patients, however, operative management was associated with reduced mortality, hospital length of stay, and overall

				costs across all age groups. The different outcomes of nonoperative versus operative management of appendicitis in older vs younger adults highlights the urgent need for a randomized trial to determine the best approach for managing appendicitis in older patients.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	Appendicitis has traditionally been treated with appendectomy, but there is growing evidence from randomized clinical trials to support nonoperative management with antibiotics for uncomplicated appendicitis.[1,2] However, randomized trials of nonoperative versus operative management have focused primarily on patients <65 years old with a limited comorbidity burden, while older adults (i.e. age 65+) have been vastly underrepresented or deliberately excluded.[1,3,4] The underrepresentation of older adults is problematic because (1) the number of Americans ≥65 years old is rapidly increasing and will soon comprise 20% of the US population, (2) although appendicitis is less common in older adults, disease incidence is still high, and (3) older adults have a higher incidence of comorbidities and frailty than younger patients so they may be more difficult to rescue from worsening infection when nonoperative management fails.[5] Consequently, it is unclear if data from existing randomized trials can adequately generalize to older adults and be used to guide therapeutic decisions.
Objectives	3	State specific objectives, including any prespecified hypotheses	5	The current study aims to evaluate outcomes of nonoperative and operative management of uncomplicated, acute appendicitis in older adults, since there is currently no data to help estimate risks in this population. Additionally, we sought to determine if the profile of risks and benefits is similar to those noted in younger patients in clinical trials. We hypothesized that, as compared to operative management,

				nonoperative management of acute appendicitis would be associated with similar morbidity and mortality but increased hospitalization length and healthcare costs for older adults, and (2) nonoperative management in older adults would have a different risk-benefit profile than for younger adults. Since prior clinical trials of nonoperative vs operative management have focused almost entirely on younger adults, this study has serious implications for whether existing data are sufficient to inform decision-making in older adults with acute, uncomplicated appendicitis, as this makes up approximately 75% of acute appendicitis cases.[6]
Methods				
Study design	4	Present key elements of study design early in the paper	6	This study is a retrospective cohort study of the National Inpatient Sample. This database provides information on an individual hospitalization and allows for in-hospital follow-up.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	After receiving approval from the Institutional Review Board of the University of Texas Southwestern, we obtained the National Inpatient Sample (NIS) database from 2004-2017.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and	6	Patients were selected based on International Classification of Disease (ICD) codes for uncomplicated, acute appendicitis (ICD-9 540 and ICD-10 K35) and only patients who survived for 24 hours after admission were included. Uncomplicated appendicitis was defined as those without perforation, abscess, or peritonitis and was selected as this mirrors prior randomized controlled trials and excludes patients with an abscess or phlegmon which would be more likely managed nonoperatively. We also excluded those <18 years, those with inflammatory bowel disease, patients who underwent a procedure but were missing dates, and those that died within 24 hours of admission. See Figure 1 for information on patient selection. In total, missing data accounted for <10% of cases.

		methods of selection of participants		
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7	*Independent variable* The exposure of interest was nonoperative versus operative management of acute appendicitis. Operative management was defined as appendectomy (identified by ICD procedure codes for laparoscopic appendectomy, open appendectomy, exploratory laparotomy, ascending colectomy, or ileocectomy) performed within 1 day of hospital admission. Nonoperative management was defined as not having surgery consistent with appendectomy performed on day 0 or 1 of hospital admission. Since appendectomy can occasionally be delayed >1 day after admission, we conducted a sensitivity analysis to avoid misclassifying patients as nonoperative. We varied the definition of operative management to include surgery within 1 day, ≤2 days, or ≤3 days after admission and repeated all analyses. Since results were consistent, the results presented are based on the original classification. *Outcomes* The primary outcome of interest was the incidence of postoperative complications: a composite variable based on previously validated of ICD-9 and ICD-10 codes that included wound complications, infection, urinary tract infection, pulmonary, gastrointestinal,

				cardiovascular, thromboembolism, cerebrovascular accident, renal failure, and bleeding.[6] For patients who underwent nonoperative management, failure of nonoperative management was also considered a complication and was defined as undergoing an appendectomy, exploratory laparotomy, colonic resection or interventional radiology drainage procedure >1 day after admission. Secondary outcomes included in-hospital mortality, length of hospitalization, and inpatient costs calculated using cost-charge ratios and inflation-adjusted to the most recent year's value.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7	(Above)
Bias	9	Describe any efforts to address potential sources of bias	7	Since appendectomy can occasionally be delayed >1 day after admission, we conducted a sensitivity analysis to avoid misclassifying patients as nonoperative. We varied the definition of operative management to include surgery within 1 day, ≤2 days, or ≤3 days after admission and repeated all analyses. Since results were consistent, the results presented are based on the original classification.
Study size	10	Explain how the study size was arrived at	6	Patients were selected based on International Classification of Disease (ICD) codes for uncomplicated, acute appendicitis (ICD9 540 and ICD10 K35) and included patients who survived for 24 hours after admission. Uncomplicated appendicitis was defined as those without perforation, abscess, or peritonitis as this mirrors prior research and excludes patients with an abscess or phlegmon which would likely be managed nonoperatively. We also

				excluded those <18 years, those with inflammatory bowel disease, patients who underwent a procedure but were missing dates, and those that died within 24 hours of admission. See Figure 1 for information on patient selection. In total, missing data accounted for <10% of cases.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	We grouped patients according to age and included an analysis with the entire cohort, those less than 65 years, and those age 65 years and above as this is a common designation for older age.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8	We grouped patients according to age and included an analysis with the entire cohort, those less than 65 years, and those age 65 years and above as this is a common designation for older age. For risk-adjustment, we used inverse probability weighting of the propensity score with regression adjustment including all variables in Table 1. We elected to use inverse probability weighting with regression adjustment because it offers a more efficient use of the data than matching, has more flexibility within the common overlap region, and the double robust property increases the chances of having an unbiased estimate in the setting of misspecification. Our balanced patient cohorts after adjusting with the propensity score are presented in Table 1 and eTable 1. *Sensitivity Analyses* Because observational study results are subject to bias from unmeasured confounding, we conducted two analyses to assess robustness of findings to the effects of an unmeasured confounder.
		(*b*) Describe any methods used to examine subgroups and interactions	10	We also assessed whether the effects of nonoperative management were different in older versus younger adults. We estimated separate regression models for outcomes in older and younger adults then compared the coefficients for the estimated treatment effects to determine whether they differed at the $p<0.05$ level, while accounting for differences in the variance-covariance matrix in each cohort via the cluster-adjusted sandwich estimator. This was done using the Stata suest command for seemingly unrelated estimation.[17,18]
		(*c*) Explain how missing data were addressed	10	Missingness in variables included in our analysis was present in <10% of cases and the missing values consisted primarily of procedure dates which are not amenable to imputation. Consequently, we conducted a complete case analysis.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	N/A	N/A

Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
(*e*) Describe any sensitivity analyses	8-9	Probabilistic sensitivity analysis First, we employed a probabilistic sensitivity analysis to assess how much an unmeasured confounder could affect results for morbidity and mortality.[7,8] For example, surgeons are presumably more likely to offer nonoperative management to patients whose age, comorbidity, frailty, or other factors would increase their risk of postoperative complications. We simulated the effects of a confounder that represented higher degrees of frailty or illness not captured by NIS variables.[9] We assumed the confounder was present in 25%-90% of the nonoperative patients, was twice as common in the nonoperative compared to the operative group, and increased relative risk of morbidity and mortality by 1.1 to 4-fold. We simulated effects of this confounder 5,000 times to estimate changes in the propensity score models. This generates a 95% simulation interval representing the most likely difference between groups after accounting for unmeasured confounding. Each simulation is a random draw from a trapezoidal distribution with a random error component so that the prevalence and strength of the confounder varied between samples within the specified ranges. This method is limited to assessing effects on categorical variables. E-value Another method of testing effects of unmeasured confounding is the e-value: the minimum strength of association between an unmeasured confounder and the outcome/exposure that could change a statistically significant result into a non-significant result (converting to the null).[10] Essentially, the e-value asks how strong an unmeasured confounder would have to be for a significant finding to be attributable to bias from the confounder rather than a real association between exposure and outcome, implying the original model would have estimated no effect if it had included the unmeasured confounder.

Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1	Figure 1
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10	We included 474,845 patients with acute, uncomplicated appendicitis. Of these, 43,846 (9.2%) underwent nonoperative management. The median age of the nonoperative cohort was 49 years (IQR 33-65) compared to 38 years (IQR 27-53) for the operative cohort (p<0.001). Patients ≥65 years old accounted for 12.9% of the sample, but 18.4% were managed nonoperatively. By contrast, nonoperative management was substantially less common (7.9%) among younger patients. Increasing comorbidity was associated with increased likelihood of nonoperative management (eTable 2).
		(b) Indicate number of participants with missing data for each variable of interest	eTable 2	eTable 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	eTable 3	eTable 3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	eTable 3	eTable 3, Figure 2A-D.

		confounders were adjusted for and why they were included		
		(*b*) Report category boundaries when continuous variables were categorized	7	We then grouped patients into those less than 65 years and those age 65 years or greater.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12	For older patients, the probabilistic sensitivity analysis (eFigure 1C) suggested that our initial results likely underestimated the morbidity reduction associated with nonoperative management, because the bias-corrected 95% simulation interval was lower than the original estimate that did not account for unmeasured confounders. Additionally, the e-value necessary to generate a null result was 2.2, indicating a result that was robust to moderate levels of unmeasured confounding. Further, since the NIS does not contain information on post-discharge outcomes, our estimates did not account for the potential effects of nonoperative failure on complication rates for the nonoperative group. To address this problem, we used a two-way deterministic sensitivity analysis and found that as long as the rate of nonoperative failure was less than 30%, there was still a morbidity benefit to nonoperative management of appendicitis in older adults. However, probabilistic sensitivity analysis suggested that the results from our propensity score analysis were susceptible to the effects of unmeasured confounding and may not represent a reliable estimate of differences. Technically, the sensitivity analysis demonstrated a 95% simulation interval >1 for nonoperative versus operative management (1.61-3.11, eFigure 2C), but the bias-corrected estimates shifted markedly closer to 1 than the propensity score analysis and the e-value needed to generate a null result was 2.4. Taken together, these results suggest that unmeasured confounding has the potential to influence our original estimate and a randomized trial could potentially show no difference.
Discussion				
Key results	18	Summarise key results with reference to study objectives	12-14	The key finding of our study is that the relative balance of risks and benefits for nonoperative versus operative management of acute appendicitis is noticeably different in older patients, compared to

				findings from prior randomized clinical trials which includes mostly younger patients. After simulating the effects of bias from unmeasured confounding in this observational cohort, nonoperative management of appendicitis in older adults was associated with (1) fewer short-term complications, (2) equivocal differences in mortality, (3) increased length of stay, and (4) greater costs when compared to appendectomy. By contrast, nonoperative management of appendicitis in younger adults was associated with no difference in morbidity, a small difference in mortality, and increased length of stay and costs (though smaller in magnitude than that seen in older adults). In short, we found that analyzing older and younger adults together obscures key differences in outcomes. This suggests that when making decisions about management of appendicitis in older adults, the surgical community should be cautious about drawing on clinical trial data from young patients with limited comorbidity burdens. Our finding is significant because we also found that nonoperative management of appendicitis has become routine for older adults, with nearly 20% being treated with antibiotics rather than surgery, twice the rate for younger patients. Since older adults are much more likely to be offered nonoperative management, the underrepresentation of these patients in clinical trials is concerning because there is a lack of evidence supporting an increasingly common clinical practice.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15	Although this study is the first to examine how age affects outcomes of nonoperative vs operative management of appendicitis, there are several limitations to acknowledge. First, although we applied rigorous techniques to account for unmeasured confounding, the accuracy of this approach depends on correctly approximating the potential effects of the confounder. It is possible that our estimates were too liberal or too conservative and did not adequately correct for bias. However, we applied two separate techniques (probabilistic sensitivity analysis and the e-value) precisely because these techniques have different underlying assumptions and could be used to triangulate estimations of bias. Second, our dataset is limited to information on the primary admission for treatment of appendicitis, so we were not able to directly evaluate differences in readmissions, post-discharge re-intervention, or missed appendiceal cancer. Consequently, we used simulation based on current published estimates to assess how this missing data might affect out conclusions. However, despite our best efforts, it is possible that these long-term differences would erase any short-term gains of nonoperative management in older adults and this might be missed by the assumptions of our simulations. As many as one third of patients initially managed with antibiotics will ultimately undergo

				appendectomy, and the rate of appendiceal cancer increases substantially with age. It is possible that these long-term differences would erase any short-term gains of nonoperative management in older adults. Due to database limitations, we were also unable to identify patients who had a fecolith, which has been shown in prior randomized trials to lead to differential outcomes with nonoperative management.[22] Further, estimation of costs via cost:charge ratios may be overly conservative and tends to miss small differences in costs between groups. Future work could more directly capture direct and indirect costs to more precisely compare nonoperative versus operative management. An additional weakness of the NIS is that we are unable to determine which aspects of care contribute to cost differences and can only perform a direct comparison of overall costs between nonoperative and operative management. Finally, it is possible that some patients who received nonoperative management were not offered surgery because their condition on admission was essentially terminal. Inclusion of such patients would artificially increase the risks of morbidity and mortality for the nonoperative group. Similarly, a patient could have been admitted with plans for appendectomy but surgery was delayed more than 24 hours after admission. Under our classification scheme, such patients would have been classified as nonoperative failures because they appeared to require surgery after initial nonoperative management. We attempted to address the misclassification problem by varying our definition of what constituted nonoperative management and by excluding patients who died within 24 hours of admission, since nonoperative management in this group was likely attributable to patient disease. These additional sensitivity analyses did not change the main study findings.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15	Overall, we found that nonoperative management was associated with reduced complications for older but not younger patients and that mortality, length of stay, and hospital costs were reduced with operative management. Our study is not meant to be a definitive description of how nonoperative and operative management compare in the treatment of acute appendicitis among older adults. Instead, we sought to conduct a comprehensive observational study to evaluate whether it was reasonable to guide management of older adults based primarily on clinical trials that studied younger adults with no comorbidities. Unsurprisingly, we found that outcomes in younger adults differ from those in older adults. This highlights the need to conduct a comprehensive randomized trial of nonoperative versus operative management of appendicitis in older adults so that

				surgeons have relevant data to use when discussing risks and benefits with these patients.
Generalisability	21	Discuss the generalisability (external validity) of the study results	15	Our use of a large, representative dataset allows for increased external validity
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18	The authors state there are no potential conflicts of interest. Dr Balentine is supported by a Paul B. Beeson Emerging Leaders Career Development Award (K76AG068515) from the National Institute on Aging. Dr. Berger acknowledges funding support from National Institutes of Health Beeson K76AG057022 and additional support from National Institutes of Health P30AG028716 and the Duke Anesthesiology Department.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

eResults. Full results from the sensitivity analysis

Nonoperative management was associated with fewer complications in older adults

When younger and older patients were analyzed together (Figure 2A), nonoperative management was not associated with a significant difference in risk-adjusted morbidity compared to operative management (risk difference -0.1%, 95% CI 0.1% to -0.4%, p=0.4). Probabilistic sensitivity analysis (eFigure 1A) was equivocal regarding whether the estimate was sensitive to bias from an unmeasured confounder that was associated with greater likelihood of receiving nonoperative management and a higher probability of postoperative complications (i.e., frailty, higher levels of comorbidity, etc.). After simulating the effects of such a confounder, the estimated 95% simulation interval for the relative risk was <1 (0.54-0.98) and did not cross 1, indicating that nonoperative management was likely to be associated with fewer complications when the analysis considered effects of unmeasured confounding. However, the simulation interval was close to 1 so it is possible that additional bias or misclassification could result in a non-significant difference between groups.

When we analyzed the cohort separately by age (<65 and ≥65 years old), the morbidity risk associated with nonoperative management was markedly different. For individuals <65 years old, nonoperative management was associated with a 0.30% increase in the incidence of postoperative complications (95% CI 0.02%-0.58%, p=0.04). By contrast, nonoperative management was associated with a 3.72% decrease in morbidity (95% CI 2.99%-4.46%, p<0.001) for patients ≥65 years old.

However, the above results were modified after accounting for potential effects of an unmeasured confounder. Sensitivity analysis suggested that results for patients <65 years old (eFigure 1B) were biased by unmeasured confounding and there was likely no difference in morbidity associated with nonoperative management since the 95% simulation interval for the relative risk crossed 1 (0.59-1.07). Similarly, the e-value of 1.3 indicated a weak unmeasured confounder was sufficient to generate a null result (no difference in morbidity) for younger patients. By contrast, sensitivity analysis for patients >65 years old (eFigure 1C) suggested that our initial results underestimated the morbidity reduction associated with nonoperative management, because the bias-corrected 95% simulation interval was lower than the original estimate that did not account for unmeasured confounders. Additionally, the e-value necessary to generate a null result was 2.2, indicating a result that was robust to moderate levels of unmeasured confounding.

In summary, an analysis that accounts for bias from unmeasured confounding differed from the original propensity score analysis and suggested that nonoperative management was associated with reduced morbidity for older adults.

Nonoperative management was associated with increased mortality

When compared to appendectomy, nonoperative management of appendicitis was associated with increased mortality for the entire cohort, and both age groups. However, the magnitude of the difference varied substantially across groups. Nonoperative management was associated with a 0.47% increase in risk-adjusted mortality (95% CI 0.40%-0.53%, p<0.001) for the entire cohort (Figure 2B). Sensitivity analysis indicated that correcting for the effects of unmeasured confounding shifted the estimated difference toward the null (eFigure 2A), though the 95% simulation interval was still >1 (95% CI 2.38-4.54). Additionally, the e-value of 8.18 suggested that a large unmeasured confounder would be needed to convert the result to the null. Overall, the sensitivity analysis and e-value suggest that the observed difference in mortality is unlikely to be explained by unmeasured confounding.

For patients < 65 years old, propensity score analysis indicated that nonoperative management was associated with a small increase in mortality (+0.29 %, 95% CI 0.23%-0.35%, p<0.001) compared to operative management. Sensitivity analysis (eFigure 2B) again suggested that this estimate was biased upward, though the 95% simulation interval for the relative risk was still >1 (95% CI 3.92-8.20) and the e-value of 14.4 indicated a very strong unmeasured confounder would be needed to convert the results to a null finding.

For patients ≥65 years old, propensity score analysis showed that nonoperative management was associated with a 1.82% increase in mortality (95% CI 2.15%-1.49%, p<0.001). However, both the probabilistic sensitivity analysis (eFigure 2C) and the e-value suggested that this result was susceptible to effects of unmeasured confounding and may not represent a reliable estimate of differences. Technically, the sensitivity analysis demonstrated a 95% simulation interval >1 for nonoperative versus operative management (1.61-3.11), but the bias-corrected estimates shifted markedly closer to 1 than the propensity score analysis and the e-value

needed to generate a null result was 2.4. Taken together, these results suggest that unmeasured confounding has the potential to influence our original estimate and a randomized trial could potentially show no difference.

Nonoperative management of appendicitis was associated with increased costs and length of stay

For the entire cohort (Figure 2C), nonoperative management was associated with a 2.88-day increase in risk-adjusted length of stay (95% CI 2.80 - 2.95, p<0.001) This difference was 2.81 days (95% CI 2.89 - 2.72, p<0.001) for patients <65 years, and 3.22 days (95% CI 3.03 - 3.41, p<0.001) for those ≥65 years old.

Nonoperative management was associated with increased hospital costs (Figure 2D) for the entire cohort ($4,477.70, 95% CI $4,216.07-$4,739.33, p<0.001), for patients <65 years, ($4,334.81, 95% CI $4,052.49-$4,617.13, p<0.001), and for patients ≥65 ($5,270.84, 95% CI $4,644.95-$5,896.73, p<0.001).

eTable 1. Standardized Differences and post-adjustment weights for the cohort following balancing using the propensity score

(Note: This does not represent the entire number of patients included in the study).

Entire Cohort				
	Propensity Weighted Cohorts		Standardized Differences[1]	
	Nonoperative Management	Operative Management	Unadjusted	Adjusted
N	231,122	233,587		
Age (years), Mean (SD)	42.3 (17.6)	42.2 (17.4)	47.56	0.60
Female Sex	116,012 (50.2)	113,638 (48.7)	10.04	3.47
Race/Ethnicity				
Caucasian	135,373 (58.6)	136,570 (58.5)		
African American	17,006 (7.4)	16,883 (7.2)	17.37	0.60
Hispanic	39,635 (17.2)	40,338 (17.3)	8.32	0.37
Asian	7,769 (3.4)	7,664 (3.3)	1.52	0.51
Native American	1,067 (0.5)	1,087 (0.5)	1.39	0.07
Other	8,584 (3.7)	8,808 (3.8)	1.47	0.36
Unknown	21,688 (9.4)	22,237 (9.5)	0.44	0.52
Income Quartile (Based on Zip Code)				
$1-$38,999	53,732 (23.3)	54,022 (23.1)		
$39,000-$47,999	54,970 (23.8)	54,960 (23.5)	1.87	0.70
$48,000-$62,999	57,025 (24.7)	57,482 (24.6)	3.52	0.16
$63,000 or more	60,402 (26.1)	62,110 (26.6)	8.70	1.18
Unknown	4,993 (2.2)	5,015 (2.2)	1.14	0.09
Primary Payer				
Medicare	32,773 (14.2)	32,061 (13.7)		
Medicaid	30,249 (13.1)	30,724 (13.2)	8.27	0.25
Private	155,430 (67.3)	157,807 (67.6)	30.37	0.42
Other	12,671 (5.5)	12,996 (5.6)	9.81	0.51
Hospital Region				0.06

Northeast	52,871 (22.9)	54,317 (23.3)		
Midwest	36,775 (15.9)	36,673 (15.7)	9.67	0.69
South	83,410 (36.1)	83,244 (35.6)	5.19	1.07
West	58,067 (25.1)	59,354 (25.4)	9.60	0.74
Hospital Size				
Small	37,360 (16.2)	36,946 (15.8)		
Medium	65,737 (28.4)	65,644 (28.1)	2.81	0.84
Large	128,026 (55.4)	130,998 (56.1)	0.27	1.53
Location/teaching status of hospital				
Rural	25,935 (11.2)	25,906 (11.1)		
Urban non-teaching	101,086 (43.7)	102,790 (44.0)	21.77	0.60
Urban teaching	104,101 (45.0)	104,892 (44.9)	20.74	0.32
Diabetes	17,442 (7.6)	16,489 (7.1)	22.71	2.35
Chronic Pulmonary Disease	19,112 (8.3)	18,859 (8.1)	18.32	0.91
Congestive Heart Failure	4,780 (2.1)	4,644 (2.0)	25.69	1.02
Hypertension			34.02	2.41
Liver Disease	4,225 (1.8)	4,076 (1.8)	18.83	1.01
Metastatic Cancer	1,735 (0.8)	1,705 (0.7)	20.73	0.84
Peripheral Vascular Disorders	2,665 (1.2)	2,491 (1.1)	15.12	1.19
Renal Failure	5,232 (2.3)	4,868 (2.1)	25.05	1.95
Patients <65 Years				
	Weighted cohorts		Standardized Differences	
	Nonoperative Management	Operative Management	Unadjusted	Adjusted
N	202,220	204,081		
Age (years), Mean (SD)	37.8 (13.2)	37.7 (13.2)	28.44	1.00
Female Sex	100,279 (49.6)	98,483 (48.3)	11.90	2.94
Race/Ethnicity				
Caucasian	113,975 (56.4)	115,223 (56.5)		

African American	15,628 (7.7)	15,327 (7.5)	19.56	0.98
Hispanic	37,775 (18.7)	38,110 (18.7)	5.14	0.07
Asian	6,495 (3.2)	6,464 (3.2)	1.60	0.28
Native American	1,002 (0.5)	997 (0.5)	1.79	0.12
Other	8,104 (4.0)	8,150 (4.0)	0.79	0.06
Unknown	19,241 (9.5)	19,810 (9.7)	9.69	0.72
Income Quartile (Based on Zip Code)				
$1-$38,999	47,614 (23.6)	47,635 (23.3)		
$39,000-$47,999	47,707 (23.6)	47,728 (23.4)	1.89	0.54
$48,000-$62,999	49,556 (24.5)	50,099 (24.6)	3.47	0.11
$63,000 or more	52,934 (26.2)	54,191 (26.6)	10.34	0.96
Unknown	4,409 (2.2)	4,428 (2.2)	1.91	0.07
Primary Payer				
Medicare	7,311 (3.6)	6,978 (3.4)		
Medicaid	29,657 (14.7)	30,142 (14.8)	16.55	0.35
Private	152,741 (75.5)	154,267 (75.6)	18.97	0.23
Other	12,511 (6.2)	12,694 (6.2)	4.35	0.54
Hospital Region				
Northeast	47,673 (23.6)	48,073 (23.6)		
Midwest	30,985 (15.3)	31,124 (15.3)	8.85	0.23
South	72,508 (35.9)	72,674 (35.6)	1.89	0.57
West	51,054 (25.3)	52,211 (25.6)	9.34	0.85
Hospital Size				
Small	32,624 (16.1)	32,097 (15.7)		
Medium	57,842 (28.6)	57,360 (28.1)	3.38	1.21
Large	111,754 (55.3)	114,624 (56.2)	0.56	1.99
Location/teaching status of hospital				
Rural	22,222 (11.0)	22,048 (10.8)		
Urban non-teaching	88,519 (43.8)	90,068 (44.1)	22.03	0.79
Urban teaching	91,479 (45.2)	91,966 (45.1)	21.55	0.38

Diabetes	11,621 (5.8)	10,921 (5.4)	19.44	2.08
Chronic Pulmonary Disease	13,928 (6.9)	13,639 (6.7)	12.98	0.97
Congestive Heart Failure	1,826 (0.9)	1,737 (0.9)	17.01	0.87
Hypertension	33,053 (16.4)	32,208 (15.8)	24.64	1.80
Liver Disease	3,358 (1.7)	3,260 (1.6)	19.72	0.71
Metastatic Cancer	933 (0.5)	912 (0.5)	18.06	0.44
Peripheral Vascular Disorders	925 (0.5)	825 (0.4)	9.15	1.11
Renal Failure	2,342 (1.2)	2,115 (1.0)	18.26	1.66

[1]Standardized differences expressed as percentages.

eTable 2. Unadjusted patient characteristics

	Missing	All patients			Patients <65 years			Patients ≥65 years		
		Non-operative Management	Operative Management	P	Non-operative Management	Operative Management	P	Non-operative Management	Operative Management	P
N		N=43,846	N=430,999		N=32,473	N=380,891		N=11,373	N=50,108	
Age (years) (IQR)	2,779 (0.6)	49 (33-65)	38 (27-53)	<0.001	42 (29-53)	36 (26-48)	<0.001	75 (68.5-81.5)	72 (67-77)	<0.001
Male Sex	7,595 (1.6)	20,443 (46.9%)	219,750 (51.9%)	<0.001	14,980 (46.1%)	196,631 (51.6%)	<0.001	5,463 (48.0%)	23,119 (46.1%)	<0.001
Race/ Ethnicity	0 (0.0)			<0.001			<0.001			<0.001
Caucasian		24,640 (56.2%)	248,435 (57.6%)		16,958 (52.2%)	213,699 (56.1%)		7,682 (67.6%)	34,736 (69.3%)	
African American		5,130 (11.7%)	28,648 (6.6%)		4,155 (12.8%)	26,505 (7.0%)		975 (8.6%)	2,143 (4.3%)	
Hispanic		6,327 (14.4%)	74,251 (17.2%)		5,450 (16.8%)	70,701 (18.6%)		877 (7.7%)	3,550 (7.1%)	
Asian		1,543 (3.5%)	13,782 (3.2%)		1,105 (3.4%)	11,827 (3.1%)		429 (3.8%)	1,955 (3.9%)	
Native American		250 (0.6%)	1,960 (0.5%)		204 (0.6%)	1,818 (0.5%)		46 (0.4%)	142 (0.3%)	
Other		1,540 (3.5%)	16,145 (3.7%)		1,248 (3.8%)	15,122 (4.0%)		292 (2.6%)	1,023 (2.0%)	
Unknown		4,425 (10.1%)	47,778 (11.1%)		3,353 (10.3%)	41,219 (10.8%)		1,072 (9.4%)	6,559 (13.1%)	
Location/ teaching status of hospital	1,361 (0.3)			<0.001			<0.001			<0.001
Rural		4,961 (11.3%)	47,201 (11.0%)		3,506 (10.8%)	40,803 (10.7%)		1,455 (12.8%)	6,398 (12.8%)	
Urban non-teaching		15,085 (34.5%)	194,878 (45.3%)		11,120 (34.2%)	171,736 (45.1%)		3,965 (34.9%)	23,142 (46.2%)	
Urban teaching		23,678 (54.2%)	187,681 (43.7%)		17,752 (54.7%)	167,241 (43.9%)		5,926 (52.1%)	20,440 (40.8%)	
Diabetes	0 (0.0)	5,707 (13.0%)	27,086 (6.3%)	<0.001	3,236 (10.0%)	18,522 (4.9%)	<0.001	2,471 (21.7%)	8,564 (17.1%)	<0.001
Chronic Pulmonary Disease	0 (0.0)	5,715 (13.0%)	32,073 (7.4%)	<0.001	3,224 (9.9%)	24,102 (6.3%)	<0.001	2,491 (21.9%)	7,971 (15.9%)	<0.001
Congestive Heart Failure	0 (0.0)	2,816 (6.4%)	6,284 (1.5%)	<0.001	938 (2.9%)	2,476 (0.7%)	<0.001	1,878 (16.5%)	3,808 (7.6%)	<0.001

Human Immuno-deficiency Virus	0 (0.0)	237 (0.5%)	511 (0.1%)	<0.001	227 (0.7%)	502 (0.1%)	<0.001	10 (0.09%)	9 (0.02%)	<0.001
Hyper-tension	0 (0.0)	15,460 (35.3%)	86,637 (20.1%)	<0.001	7,991 (24.6%)	56,444 (14.8%)	<0.001	7,469 (65.7%)	30,193 (60.3%)	<0.001
Liver Disease	0 (0.0)	2,018 (4.6%)	6,009 (1.4%)	<0.001	1,508 (4.6%)	4,970 (1.3%)	<0.001	510 (4.5%)	1,039 (2.1%)	<0.001
Metastatic Cancer	0 (0.0)	1,392 (3.2%)	1,855 (0.4%)	<0.001	747 (2.3%)	1,042 (0.3%)	<0.001	645 (5.7%)	813 (1.6%)	<0.001
Peripheral Vascular Disorders	0 (0.0)	1,262 (2.9%)	3,635 (0.8%)	<0.001	356 (1.1%)	1,260 (0.3%)	<0.001	906 (8.0%)	2,375 (4.7%)	<0.001
Renal Failure	0 (0.0)	2,814 (6.4%)	6,678 (1.5%)	<0.001	1,104 (3.4%)	3,042 (0.8%)	<0.001	1,710 (15.0%)	3,636 (7.3%)	<0.001
Solid Tumor without Metastasis	0 (0.0)	2,498 (5.7%)	5,107 (1.2%)	<0.001	1,261 (3.9%)	2,868 (0.8%)	<0.001	1,237 (10.9%)	2,239 (4.5%)	<0.001
Weight Loss	0 (0.0)	2,282 (5.2%)	2,714 (0.6%)	<0.001	1,128 (3.5%)	1,433 (0.4%)	<0.001	1,154 (10.2%)	1,281 (2.6%)	<0.001
Number of Comorbid-ities	0 (0.0)			<0.001			<0.001			<0.001
0		15,076 (34.4%)	267,020 (62.0%)		14,071 (43.3%)	256,301 (67.3%)		1,005 (8.8%)	10,719 (21.4%)	
1		9,797 (22.3%)	93,177 (21.6%)		7,746 (23.9%)	79,038 (20.8%)		2,051 (18.0%)	14,139 (28.2%)	
2		7,411 (16.9%)	40,695 (9.4%)		4,945 (15.2%)	29,204 (7.7%)		2,466 (21.7%)	11,491 (22.9%)	
3		4,911 (11.2%)	17,312 (4.0%)		2,764 (8.5%)	10,412 (2.7%)		2,147 (18.9%)	6,900 (13.8%)	
4+		6,651 (15.2%)	12,795 (3.0%)		2,947 (9.1%)	5,936 (1.6%)		3,704 (32.6%)	6,859 (13.7%)	
Hospital Region	0 (0.0)			<0.001			<0.001			<0.001
Northeast		10,186 (23.2)	98,135 (22.8)		7,521 (23.2)	88,345 (23.2)		2,665 (23.4)	9,790 (19.5)	
Midwest		8,332 (19.0)	65,450 (15.2)		5,954 (18.3)	56,783 (14.9)		2,378 (20.9)	8,667 (17.3)	
South		15,660 (35.7)	150,965 (35.0)		11,802 (36.3)	133,828 (35.1)		3,858 (33.9)	17,1377 (34.2)	
West		9,668 (22.1)	116,449 (27.0)		7,196 (22.2)	101,935 (26.8)		2,472 (21.7)	14,514 (29.0)	

eTable 3. Bivariate results of outcomes

	All patients			Patients <65 years			Patients ≥65 years		
	Non-operative management	Operative management	P value	Non-operative management	Operative management	P value	Non-operative management	Operative management	P value
Incidence of any hospital complication	2,836 (6.5%)	24,372 (5.7%)	<0.001	1,802 (5.6%)	18,097 (4.8%)	<0.001	1,034 (9.1%)	6,275 (12.5%)	<0.001
In-Hospital Mortality	736 (1.7%)	689 (0.2%)	<0.001	255 (0.8%)	196 (0.05%)	<0.001	481 (4.2%)	493 (1.0%)	<0.001
Disposition			<0.001			<0.001			<0.001
Home	37,705 (86.0%)	422,577 (98.1%)		27,724 (85.4%)	371,770 (97.6%)		6,279 (55.2%)	40,520 (80.9%)	
Transfer to Other Facility	4,629 (10.6%)	6,691 (1.6%)		4,465 (13.8%)	8,712 (2.3%)		4,597 (40.4%)	9,067 (18.1%)	
Died in Hospital	736 (1.7%)	689 (0.2%)		255 (0.8%)	196 (0.05%)		481 (4.2%)	493 (1.0%)	
Length of Stay (Days) (IQR)	4 (2-8)	2 (1-3)	<0.001	4 (2-12)	2 (1-3)	<0.001	6 (3-10)	3 (2-6)	<0.001
Cost ($) (IQR)	8,924.15 (4,964.96-16,169.88)	7,593.94 (5,809.20-10,223.77)	<0.001	8.275.36 (4,688.04-14,551.25)	7,397.24 (5,695.42 - 9,815.32)	<0.001	11,283.21 (6,052.98-21,756.13)	9,700.85 (7,111.45-14,169.20)	<0.001
Infectious Complication	583 (1.3%)	3,215 (0.7%)	<0.001	391 (1.2%)	2,574 (0.7%)	<0.001	192 (1.7%)	641 (1.3%)	<0.001
Urinary Complication	118 (0.3%)	2,011 (0.5%)	<0.001	77 (0.2%)	1,452 (0.4%)	<0.001	41 (0.4%)	559 (1.1%)	<0.001
Pulmonary Complication	393 (0.9%)	3,300 (0.8%)	<0.001	231 (0.7%)	2,437 (0.6%)	0.1	162 (1.4%)	863 (1.7%)	0.03
Cardio-vascular Complication	231 (0.5%)	1,622 (0.5%)	<0.001	108 (0.3%)	874 (0.2%)	<0.001	123 (1.1%)	748 (1.5%)	<0.001
Thrombo-embolic Complication	134 (0.3%)	568 (0.1%)	<0.001	78 (0.2%)	370 (0.1%)	<0.001	56 (0.5%)	198 (0.4%)	0.1

Acute Renal Failure	114 (0.3%)	1,949 (0.5%)	<0.001	75 (0.2%)	1,415 (0.4%)	<0.001	39 (0.3%)	534 (1.1%)	<0.001