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Prescription Medication Use According to Body Weight Classification for a Large Employer in the United States

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Objectives To identify the extent that body mass index is associated with the frequency and cost of 32 selected prescribed medications.

Methods Retrospective analysis of prescription medication use among 2531 workers employed all four academic years for a large employer in the United States, 2011-2014. Pharmaceutical and other data were available on each employee.

Results Those completing wellness screening were more likely women and younger. They were also significantly more likely to file a pharmaceutical claim each year. Higher body weight was significantly associated with a greater number of prescription claims for 11 of 32 (overweight vs. normal weight) and 21 of 32 (obese vs. normal weight) medications. The strongest positive association between body weight and prescription medications was for diabetes, high cholesterol, high blood pressure, and edema. Higher body weight was associated with less prescription medication for birth control, herpes, and osteoporosis. Pharmaceutical costs tend to increase with weight. For example, annual total cost for obese compared with normal weight individuals was significantly higher for acid reflux, anticonvulsants, asthma, depression, diabetes, edema, high blood pressure, muscle spasms, nausea/vomiting, opioids, statins, and thyroid, but significantly lower for birth control, herpes, and osteoporosis.

Conclusions This study shows an association between BMI and pharmaceutical costs for a large employer.

Strengths and limitations of this study

- Research has shown that obesity increases the use and cost for medications related to the cardiovascular system, gastrointestinal system, respiratory system, central nervous system, endocrine system, and more. The current study assessed the association between body mass index, primarily obesity, and several types of prescription medication, more than previously considered.

- Some associations previously observed were confirmed, but a few were not found to be significant in our study. Some new associations were identified, which were not previously considered, including three in which obesity was associated with lower use and cost of medication.
- The study design did not allow us to determine whether heavier weight led to medication use or medication use led to greater weight.
- The study population and patterns of prescription drug use may limit generalization of the results.

Introduction

Many companies offer wellness screening programs such as biometric screenings and health risk assessments (questionnaires that ask about lifestyle, physical, and psychological health) to their employees. The 2016 Employer Health Benefits Survey found that among large firms (200 or more employees) in the United States, 59% offered health risk assessment (of which 32% had an incentive component) and 53% offered biometric screening (of which 31% included an incentive component).[1] These programs are intended to promote a greater sense of personal responsibility for lifestyle choices, identify the need for health behavior change, reduce future health problems, encourage patient management of existing health problems, decrease worker absenteeism, and improve job satisfaction and worker productivity.[2-7]

Pharmaceuticals are often useful for preventing and managing health problems. For example, antihypertensive medication, or statins, are useful in preventing cardiovascular disease;[8-10] multivitamins or folic acid for preventing congenital abnormalities;[11] aspirin and non-steroidal anti-inflammatory for preventing colorectal cancer;[12] bronchodilators, steroids, and anti-inflammatories for managing asthma;[13] and nonsteroidal anti-Inflammatory drugs, steroids, analgesics, and immunosuppressive drugs for managing arthritis.[14] Consequently, wellness screening may actually increase use of prescription medication.[15] In addition to the benefits of managing existing health problems, longer-term pharmaceutical costs associated with more serious health problems may be avoided.

Although obesity is associated with increased risk for various chronic health conditions and poorer health-related quality of life,[16,17] only in the last 15 years or so has its impact on healthcare expenditures been assessed.[18] Further, only a small number of studies have explored the association between body weight and prescription drug use. A study conducted in England found that overweight and obese individuals were more likely to receive medication for the cardiovascular system; gastrointestinal system; respiratory system; central nervous system; endocrine system; gynecology/urinary disorders; musculoskeletal and joint disorders; infections; eye, ear and oropharynx problems; and skin disorders.[19] A study in Sweden showed that use and cost of medication in general are significantly greater in obese individuals.[20] A study in the United States found that obesity was responsible for $7 billion in Medicare prescription drug costs in 2006.[21] Another study conducted in the United States identified increased medication use during 1988 through 2012, with the increase most prominent among obese individuals.[22] A large cross-sectional study of 9789 adults in the National Health and Nutrition Examination Survey (NHANES) found that obese individuals utilize several prescription drugs (e.g., hypertension, lipid-lowering, and diabetes medications) more frequently than normal weight individuals.[23] Another study based on NHANES data found that while medication use increased over time for obese compared with normal weight individuals ages 40 years and older, the increase was only marginal for those aged 25-39 years.[24] One study found that obese individuals used more analgesic, asthma, cardiovascular, diabetes, intranasal allergic rhinitis, thyroid, and ulcer medications.[25]

The purpose of this study is to identify the extent that body mass index is associated with the frequency and total cost of 32 more commonly prescribed medications among employees. These employees participated in wellness screening, which provided information about body mass. Although studies have previously looked at the association between body mass index (BMI) and prescription medications, we evaluate some drugs that have not been previously considered, and the breadth of drugs covered is greater than in previous studies.

Methods

Analyses are based on employees of a large school district in the western United States involving 6 high schools, 8 junior high schools, and 31 elementary schools. The study involved the academic years 2010-11, 2011-12, 2012-13, and 2013-14. Employees were offered wellness screenings (personal health risk assessment and biometric evaluation) each fall. Pharmaceutical claims data was also obtained for the employees in each academic year. Wellness screening and pharmaceutical claims data were combined with an eligibility file of employees and assessed within each academic year. The eligibility file contained information on current employment, age, sex, and year.

Wellness Screening

Wellness screening consisted of a personal health risk assessment (HRA) and biometric evaluation. All employees were offered wellness screening. Although participation was voluntary, it was promoted through incentives. The HRA involved 36 questions. For the current study, we only used information on self-rated health status, exercise, sleep, stress, fruit consumption, vegetable consumption, and grain consumption. Self-rated health was based on the question: "In general, how would you rate your overall health?" Participants responded on a scale from 1 (low) to 10 (high). Exercise was based on the question: "During the past week, how many days per week do you usually exercise?" Sleep was based on the question: "During the past week, how many days did you get enough sleep so that you awoke feeling rested and refreshed?" Stress was based on the question: "During the past 3 months, how often has your normal daily routine been disrupted by stressful events? Fruit, vegetables, and grain consumption, were determined as the number of servings per day.

Biometric screenings included measurements of body mass, blood pressure, cholesterol, and glucose. They were provided at no cost to the employees and were made available to employees on location or with a personal physician. A health nurse or physician assisted the employee in interpreting their biometric measures. The current study only considers BMI. Weight classifications are determined as follows: normal weight (BMI < 25), overweight (BMI 25-29), and obese (BMI 30+).

Pharmaceutical Claims Data

Pharmaceutical costs were adjusted to account for medical-cost inflation. Tom's Medical-Cost Inflation Calculator was used for this purpose. Annual average dollar ($) pharmaceutical cost and number of claims per eligible employee were obtained. In this study, cost represents the amount paid by the company as well as copays by the employee.

Statistical Techniques

Counts, means, standard deviations, standard errors, and percentages were used to describe characteristics of the study population. Regression and Pearson's Correlation Coefficients were used to evaluate the association between selected variables. Because the use of pharmaceuticals tends to be greater in older employees and among women,[26,27] we will adjust for these variables, along with year. Risk ratios were used to assess medication use for selected drugs according to weight classification. These ratios were adjusted using the Mantel-Haenszel method. Statistical significance was assessed using the p value and 95% confidence limits. Two-sided tests of significance were based on the 0.05 level against a null hypothesis of no association. Data was evaluated using the statistical software package PC-SAS (version 9.4;SAS Institute, Inc., 2014)

Results

In 2010-11, there were 3023 eligible employees, of which 2531 (83.72%) remained employed through the academic year 2013-14. The percentage of females was about the same for those remaining employed versus not, at about 73.2%. Mean age was 6.3 (SE = 0.2, p < 0.0001) years older for those continuously employed, averaging about 48.4 (SD = 10.4, range 18-78). The results of this study are based on those continuously employed over the four academic years.

Most employees participated in annual wellness screening (84.1% in 2010-11, 84.4% in 2011-12, 87.6% in 2012-13, and 80.7% in 2013-14). Women were 1.04 (95% CI 1.02- 1.06) times more likely than men to complete annual wellness screenings, after adjusting for age and year. Participants in wellness screening were significantly younger, on average (47.7 vs. 49.8, p < 0.0001), after adjusting for sex and year. Those participating in wellness screening filed more pharmaceutical claims annually (M = 10.6 vs. 9.6, $p = 0.0064$), but there was no significant difference in mean annual total costs, after adjusting for age, sex, and year.

Participants in wellness screenings were asked how they would rate their overall health. This variable was regressed on BMI, exercise, fruit, vegetables, grains, stress, sleep, age, sex, and year. The variability in self-rated overall health was most strongly associated with BMI (13.8%, $p < 0.0001$), followed by days exercised per week (8.6%, $p < 0.0001$), and days of restful sleep per week (3.6%, $p < 0.0001$). Body mass was significantly correlated with exercise ($r = -0.21$, $p < 0.0001$), fruit ($r = -0.04$, $p = 0.0146$), vegetables ($r = -0.05$, $p = 0.0013$), grains ($r = -0.05$, $p = 0.0030$), stress ($r = 0.05$, $p = 0.0014$), and sleep (-0.06, $p < 0.0001$), after adjusting for age, sex, and year.

The mean health rating was 8.4 for normal weight (BMI 18-24), 7.9 for overweight (BMI 25-29), and 7.1 for obese (BMI 30+), after adjusting for age, sex, and year. The percentage of men and women in each of these BMI categories is presented in Table 1. Frequency and total cost of pharmaceuticals increased with increasing weight for men and women. The distribution of mean frequency and particularly total cost values are highly skewed, as indicated by their comparison with the median scores.

The association between weight and annual frequency and total cost of pharmaceutical claims is shown in Table 2. Overweight compared with normal weight participants were 1.10 times more likely to file 15 or more pharmaceutical claims per year versus no claims. Obese compared with normal weight participants were 1.27 times more likely to file 15 or more pharmaceutical claims per year versus no claims. Overweight compared with normal weight participants were 1.08 times more likely to have annual pharmaceutical costs of $1000 or more per year than no costs. Obese compared with normal weight participants were 1.20 times more likely to have annual pharmaceutical costs of $1000 or more per year than no costs.

Overweight and obese individuals are significantly more likely to file a claim each year for many types of medication (Table 3). Overweight individuals are significantly more likely than normal weight individuals to file a claim for 11 of the 32 medications considered. Obese individuals are more likely than normal weight individuals to file a claim for 21 of the selected medications. The strongest positive association between weight and prescription medications is for diabetes, high cholesterol, high blood pressure, and edema. Overweight individuals were less likely to receive medication for birth control or osteoporosis. Higher body weight lowers the need for medications associated birth control, herpes, and osteoporosis. For all prescription medications, obese are 1.05 (95% CI 1.02-1.07) times more likely than normal weight individuals to file a claim (population attributable fraction 3.77), adjusting for age, sex, and year.

We also report the population attributable fraction (population attributable risk percent) in the table. For example, this statistic says that 3.78% of diabetes medication is attributed to being overweight and 6.62% of diabetes medication is attributed with being obese. Where the risk ratio is less than 1, we estimated the preventive fraction. For example, 15% more birth control medication would have been prescribed in the absence of obesity. However, these statistics imply a cause-and-effect association between exposure and disease.

Annual total cost for the selected medications according to weight classification is shown in Table 4. Pharmaceutical cost tends to increase with weight. Overall, obese individuals have significantly greater annual total cost than normal weight individuals. Annual total cost for obese individuals is significantly greater than normal weight individuals for acid reflux, anticonvulsants, asthma, depression, diabetes, edema, high blood pressure, muscle spasms, nausea/vomiting, opioids, statins, and thyroid. Annual total cost for obese individuals is significantly greater than overweight individuals for anticonvulsants, diabetes, high blood pressure, inflammation, muscle spasms, and thyroid. On the other hand, annual total cost for obese individuals is significantly lower than normal weight individuals for birth control, herpes, and osteoporosis. Annual total cost for obese individuals is significantly lower than overweight individuals for herpes. The average annual total cost for all prescription medications was 691.4 for normal weight, 843.2 for overweight, and 910.9 for obese, adjusting for age, sex and year. The difference between normal weight and obese was significant ($p = 0.0208$).

Discussion

The current study identified the degree to which increasing body weight is associated with frequency and cost of 32 types of medication. We found positive associations between body weight and higher use of medications for treating acid reflux, arthritis, asthma, bacterial infections, cardiovascular disease, blood coagulation, colds, flu, allergies, depression, diabetes, edema, high blood pressure, inflammation, muscle spasms, pain, stomach acid, thyroid, and ulcers. Other studies have identified a similar association between body weight and some of the medications used to treat these conditions.[19, 22, 23, 25] Obese individuals were also more likely to be prescribed vitamins and minerals. We did not find an association between body weight and increased use of medication for the bowel/rectum, skin, or urinary tract, which was counter to that found in other studies.[19, 28-30] We also assessed but did not find a significant association for medications used to treat anxiety, fungus, seizures, or teeth and gums, although the number receiving medication for teeth and gums were small. Finally, we assessed the association between body weight and medications used to treat birth control, herpes, and osteoporosis, for which significant negative associations were found. We are not aware of other studies that have looked at the association between body weight and medications used for coagulation of blood, colds, flu, depression, edema, birth control, herpes, or osteoporosis.

For those medications in which there was a significant positive or negative association with body weight, some showed no significant association with annual total cost. This was the case for bacterial infections, coagulation of blood, eye infection, and ulcers. This is likely due to the high variability in the annual total cost data. For bacterial infections, the coefficient of variation is 6.1 for normal weight, 14.4 for overweight, and 4.3 for obese; for coagulation of blood the coefficient of variation is 29.7 for normal weight, 37.4 for overweight, and 11.6 for obese; for eye infection, the coefficient of variation is 6.2 for normal weight, 4.8 for overweight, and 5.1 for obese; and for ulcers, the coefficient of variation is 14.6 for normal weight, 20.6 for overweight, and 10.8 for obese. In addition, the increased use of medication among those with bacterial or eye infections was relatively small.

Increased use of medication for acid reflux or stomach acid among obese individuals is consistent with previous research that showed greater reflux disease hospitalization rates with higher BMI.[31, 32] Another study found that higher BMI is associated with increased gastroesophageal reflux in both normal and overweight individuals.[33] Greater weight can add pressure to the stomach and diaphragm, thereby resulting in reflux. Further, increased use of medication for nausea/vomiting among obese individuals is consistent with other research associating increasing BMI with nausea/vomiting.[34]

The positive association between being overweight or obese with increased use of medication for ulcers is consistent with other research, particularly peptic (gastric and duodenal) ulcers.[35, 36] The mechanism to explain the association between obesity and peptic ulcer disease remains unclear. Obesity is also associated with Helicobacter pylori, which has been linked with gastric ulcers.[37]

Overweight and obese individuals had a higher use of medication for inflammation. Overweight and especially obese individuals are at greater risk for chronic inflammation, which can compromise the immune system. As such, overweight and obese individuals are at greater risk for infections.[38-40] This is consistent with our results that show increased use of antibiotics and medication for eye infections among obese individuals. However, research has shown that antibiotics can also weaken the immune system,[41] as well as lead to obesity.[42] Some chronic inflammatory diseases known to be associated with obesity in which we found a positive association between obesity and medication included influenza,[43, 44] heart disease,[45] diabetes,[46] allergies,[47-50] asthma,[51] edema,[52-54] and arthritis.[55-58] A compromised immune system may also trigger autoimmune diseases, including rheumatoid arthritis and thyroid disease,[59] as indicated in the current study.

Overweight and obese individuals were more likely to receive cold, flu, or allergy medication. Obesity is associated with impaired immune response to influenza vaccination in humans.[60] Because vaccination is less successful for obese individuals, a greater level of medication may be sought for treating colds, flu, and allergies.

Overweight and obese individuals received higher levels of pain medication. Research indicates that the nature of the relationship between higher BMI and pain is likely indirect.[61] For example, greater body weight is associated with osteoarthritis, which, in turn, leads to pain.[62] Being overweight or obese may result in greater risk for back pain, joint pain, and muscle spasms.[63] One study also found that obese individuals were more sensitive than those of normal weight to pressure pain.[64]

We found that overweight and obese individuals were more likely to receive depression medication than those of normal weight. This is consistent with previous research.[65-68] The age-adjusted percentage of adults in the United States ages 20 years and older who were obese was 43.2 for those with depression compared with 33.0 for those with no depression.[69] It may be that higher use of prescription medication for depression among overweight and obese individuals is because these people are more likely to experience other conditions related to depression, such as heart disease and diabetes.[70-72]

Obese individuals filed more claims for vitamins and minerals. Previous research has associated low vitamin B12 with being overweight or obesity.[73] Vitamin B assists the body in metabolizing fats, carbohydrates, and protein, as well as helps with appetite control. Deficiency in vitamin B can cause anemia or nervous conditions. Another study found that the prevalence of vitamin D deficiency was 35% greater in obese individuals.[74] Vitamin D assists the body to absorb calcium and promote bone growth, whereas deficiency causes soft bones and depression. Among the vitamin or mineral claims filed in the current study, 8.0% involved vitamin B and 57.3% involved vitamin D.

References

1. 2016 Employer Health Benefits Survey. kff.org. http://www.kff.org/health-costs/report/2016-employer-health-benefits-survey/. Published September 14, 2016. Accessed February 21, 2018.
2. Chen L, Hannon PA, Laing SS, Kohn MJ, Clark K, Pritchard S, Harris JR. Perceived workplace health support is associated with employee productivity. Am J Health Promot. 2015;29(3):139-146.

3. Centers for Disease Control and Prevention. cdc.gov. http://www.cdc.gov/sustainability/worksitewellness/ Worksite wellness. Updated December 9, 2014. Accessed March 18, 2018.

4. Michaels CN, Greene AM. Worksite wellness: increasing adoption of workplace health promotion programs. Health Promot Pract. 2013;14(4):473-479.

5. Witt LB, Olsen D, Ablah E. Motivating factors for small and midsized businesses to implement worksite health promotion. Health Promot Pract. 2013;14(6), 876-884.

6. Niessen MA, Kraaijenhagen RA, Dijkgraaf MG, van Pelt D, van Kalken CK, Peek N. Impact of a Web-based worksite health promotion program on absenteeism. J Occup Environ Med. 2012;54(4):404-408.

7. Kaspin LC, Gorman KM, Miller RM. Systematic review of employer-sponsored wellness strategies and their economic and health-related outcomes. Popul Health Manag. 2013;16(1): 14-21.

8. Karmali KN, Lloyd-Jones DM, Berendsen M, et al. Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. JAMA Cardiol. 2016;1(3):341-349.

9. Fretheim A, Odgaard-Jensen, Brørs O, Madsen S, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.

10. Taylor F, Huffman MD, Macedo A, et al. Statins for the primary prevention of cardiovascular disease. Cochrane. 2013. http://www.cochrane.org/CD004816/VASC_statins-primary-prevention-cardiovascular-disease. Accessed February 21, 2018.

11. Czeizel AE. Birth defects are preventable. Int J Med Sci. 2005;2(3):91-92.

12. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029-2043.

13. Asthma. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660. Published March 9, 2018. Accessed February 24, 2018.

14. Arthritis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/arthritis/diagnosis-treatment/drc-20350777. Published March 7, 2018. Accessed February 24, 2018.

15. Preventive Medicine Reports Paper

16. Thompson D, Edelsberg J, Colditz GA, Bird AP, Oster G. Lifetime health and economic consequences of obesity. Arch Intern Med. 1999;11;159(18):2177-2183.

17. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009;121(6):21-33.

18. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Int J Obes. 2005;29(3):334-9.

19. Kinge JM, Morris S. Association between obesity and prescribed medication use in England. Econ Hum Biol. 2014;15:47-55.

20. Narbro K, Agren G, Jonsson E, et al. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. Arch Intern Med. 2002;162(18):2061-2069.

21. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff. 2009;28(5):w822-31.

22. Randhawa AK, Parikh JS, Kuk JL. Trends in medication use by body mass index and age between 1988 and 2012 in the United States. PLoS One. 2017 Sep 20;12(9):e0184089.

23. Kit BK, Ogden CL, Flegal KM. Prescription medication use among normal weight, overweight, and obese adults, United States, 2005-2008. Ann Epidemiol. 2012;22(2):112-9.

24. Jarrett B, Bloch GJ, Bennett D, Bleazard B, Hedges D. The influence of body mass index, age and gender on current illness: a cross-sectional study. Int J Obes. 2010;34(3):429-36.

25. Raebel MA, Malone DC, Conner DA, Xu S, Porter JA, Lanty FA. Health services use and health care costs of obese and nonobese individuals. Arch Intern Med. 2004;164(19):2135-40.

26. Metge C, Black C, Peterson S, Kozyrskyi AL. The population's use of pharmaceuticals. Med Care. 1999;37(6 Suppl):JS42-JS59.

27. Bertakis K, Azari R, Helms L, Callahan E, Robbins J. Gender differences in the utilization of health care services. J Fam Pract. 2000;49(2):147-152.

28. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One 2013;8(1):e53916.

29. Brown J, Wimpenny P, Maughan H. Skin problems in people with obesity. Nurs Stand. 2004;18(35):38-42.

30. Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. Urology. 2012;79(2):266-9.

31. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup Study. First National Health and Nutrition Examination Survey. Ann Epidemiol. 1999;9(7):424-35.

32. Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Alim Pharmacol Ther. 2013;37(5):555-563.

33. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Association between body mass index and gastroesophageal reflux symptoms in both normal weight and overweight women. N Engl J Med. 2006;354(22)2340-2348.

34. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol 2004;99(9):1807-1814.

35. Boylan MR, Khalili H, Huang ES, Chan AT. Measures of adiposity are associated with increased risk of peptic ulcer. Clin Gastroenterol Hepatol. 2014 Oct;12(10):1688-1694.

36. Kim J, Kim KH, Lee BJ. Association of peptic ulcer disease with obesity, nutritional components, and blood parameters in the Korean population. PLoS One. 2017;12(8): e0183777.

37. Xu M, Liu L, Yuan B, Yin J, Lu Q. Association of obesity with Helicobacter pylori infection: A retrospective study. World J Gastroenterol 2017;23(15):2750-2756.

38. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006;6(7)438-46.

39. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes. 2013;37:333-340.

40. Lübbeke A, Zingg M, Hoffmeyer P, et al. Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthopaedica. 2016;87(2):132-138

41. Yang JH, Bhargava P, McCloskey D, Mao N, Palsson BO, Collins JJ. Antibiotic-induced changes to the host metabolic environment inhibit drug efficacy and alter immune function. Cell Host & Mocrobe. 2017;22(6):757-765.

42. Early G. Current Evidence regarding antibiotic exposure and childhood obesity: an integrative review. Ped Nurs. 2017;43(4):169-174.

43. Bandaru P, Rajkimar H, Napanveettil G. The impact of obesity on immune response to infection and vaccine: an insight into plausible mechanisms. Endocrinol Metab Synd 2013;2:2.

44. Kwong JC, Campitelli MA, Rosella LC. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada: a cohort study. Clin Infect Dis. 2011;53(5):413-421.

45. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010;2010:535918.

46. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.

47. Ciprandi G, Pistorio A, Tosca M, Ferraro MR, Cirillo I. Body mass index, respiratory function and bronchial hyperactivity in allergic rhinitis and asthma. Respir Med 2009;103(2):289-295.

48. Gorgievska-Sukarovska B, Lipozencić J, Susac A. Obesity and allergic diseases. Acta Dermatovenerol Croat. 2008;16(4):231-235.

49. Shah R, Yang Y. Health and economic burden of obesity in elderly individuals with asthma in the United States. Popul Health Manag 2015;18(3):186-91.

50. Guo Y, Moon JY, Laurie CC, et al. Genetic Predisposition to Obesity is associated with Asthma in US Hispanics/Latinos: Results from the Hispanic Community Health Study/Study of Latinos. Allergy. 2018;doi: 10.1111/all.13450. [Epub ahead of print]

51. Rodriguez D. Obesity and Asthma – What's the Connection. https://www.everydayhealth.com/asthma/obesity-connection.aspx. Published August 28, 2013. Accessed April 12, 2018.

52. Greene, A.K., et al. Lower-Extremity Lymphedema and Elevated Body-Mass Index. N Engl J Med. 2012;366:2136-2137.

53. Helyer, L.K., et al. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. Breast J. 2012;16(1):48-54.

54. Greene AK, Grant FD, Slavin SA, Maclellan RA. Obesity-induced lymphedema: clinical and lymphoscintigraphic features. Plast Reconstr Surg. 2015;135(6):1715-1719.

55. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138(2):185-193.

56. Baodong Qin, Min Yang, Haitao Fu, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17(1):86.

57. Feng J, Chen Q, Yu F, et al. Body mass index and risk of rheumatoid arthritis: a meta-analysis of observational studies. Medicine. 2016;95(8):e2859.

58. Albrecht K, Richter A, Callhoff J, et al. Body mass index distribution in rheumatoid arthritis: a collaborative analysis from three large German rheumatoid arthritis databases. Arthritis Res Ther. 2016;18:149.

59. Rodriguez D. How Your Immune System Worsens Arthritis. EverydayHealth.com. https://www.everydayhealth.com/arthritis/understanding/the-immune-system.aspx. Published August 1, 2012. Accessed April 11, 2018.

60. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes. 2012;36(8):1072-1077.

61. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8:399-408.

62. Erdmann J. Osteoarthritis and Obesity. www.arthritis.org. https://www.arthritis.org/living-with-arthritis/comorbidities/obesity-arthritis/osteoarthritis-and-obesity.php. Accessed April 11, 2018.

63. American Obesity Association. Health effects of obesity. AOA Fact Sheets. 2002.

64. Tashani OA, Asitita R, Sharp D, Johnson MI. Body mass index and distribution of body fat can influence sensory detection and pain sensitivity. Eur J Pain 2017;21(7):1186-1196.

65. Rathee N. Obesity and depression: Are they related? Indian J Health Well. 2017;8(12):1472-1475.

66. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. Int J Obesity. 2009;33(2):257-266.

67. Onyike CU, Crum RM, Lee HB, Lyketsos DG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003;158(12):1139-1147.

68. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2008;70(3):288-297.

69. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005-2010. NCHS Data Brief, No. 167, October 2014.

70. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry 2004;65(5):634-651.

71. Ferraro KF, Su Y, Gretebeck RJ, Black DR, Badylak SF. Body mass index and disability in adulthood: A 20-year panel study. Am J Public Health. 2002;92(5):834-840.

72. Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. J Psychosom Res. 2002;53(4):859-863.

73. Baltaci D, Kutlucan A, Turker Y, et al. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Med Glas. 2013;10(2):203-210.

74. Pereira-Santos M[1], Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341-349.

Footnotes

Contributors: RMM conceived and designed the epidemiological study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. RPF interpreted the data, provided a literature review, and revised the manuscript. Both authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by both authors.

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Table 1 Mean Frequency and Total Cost of Pharmaceuticals According to Classifications of Body Mass Index and Sex in Wellness Screening Participants

	Men							Women						
Weight		Frequency Mean			Total Cost Mean				Frequency Mean			Total Cost Mean		
	%	Mean	Pr > |t|	Median	Mean	Pr > |t|	Median	%	Mean	Pr > |t|	Median	Mean	Pr > |t|	Median
Normal weight BMI < 25	21.0	6.3	< .0001	2	744.3	0.7844	23.3	44.2	10.5	< .0001	7	900.0	0.0431	216.0
Overweight BMI 25-29	42.3	7.9	< .0001	4	746.5	0.7979	66.1	28.5	13.2	0.0003	8	1005.1	0.3032	255.7
Obese BMI 30+	36.6	10.2	0.0000	5	813.1	0.0000	81.6	27.2	15.0	0.0000	11	1137.3	0.0000	320.3
P value				< 0.001			< 0.001				< 0.001			< 0.0001

Means are adjusted for age and year. Differences in the median values were assessed for statistical significance using the median one-way analysis chi-square test.

Table 2. Frequency and Total Cost of Pharmaceutical Medication for Overweight and Obese Compared with Normal Weight Participants in Wellness Screening

Frequency								Total Cost							
		Overweight vs Normal Weight			Obese vs Normal Weight					Overweight vs Normal Weight			Obese vs Normal Weight		
No.	%	Risk Ratio	95% LCL	95% UCL	Risk Ratio	95% LCL	95% UCL	$	%	Risk Ratio	95% LCL	95% UCL	Risk Ratio	95% LCL	95% UCL
0	21.64	0.00			0.00			0	21.64	0.00			0.00		
1-4	20.62	0.96	0.89	1.05	0.94	0.85	1.02	1-99	21.33	0.97	0.89	1.05	0.99	0.91	1.07
5-9	17.14	0.92	0.84	1.01	0.94	0.85	1.03	100-499	25.31	0.99	0.93	1.07	1.10	1.03	1.18
10-14	13.03	1.06	0.94	1.18	1.17	1.05	1.31	500-999	11.67	1.05	0.93	1.18	1.21	1.07	1.36
15+	27.57	1.10	1.03	1.18	1.27	1.20	1.36	1000+	20.05	1.08	1.00	1.18	1.20	1.11	1.30

LCL: Lower Confidence Level; UCL: Upper Confidence Level. Risk ratios and confidence intervals adjusted for age, sex, and year.

Table 3. Medication Use According to Weight Classification in Wellness Screening Participants

		Overweight vs Normal Weight				Obese vs Normal Weight			
Medication	%	Risk Ratio	95% LCL	95% UCL	Population Attributable Fraction	Risk Ratio	95% LCL	95% UCL	Population Attributable Fraction
Acid Reflux	5.43	1.23	0.96	1.57		1.69	1.34	2.12	3.61
Antibiotic	20.98	1.03	0.93	1.15		1.16	1.04	1.29	3.25
Anticonvulsants	1.38	0.82	0.48	1.40		1.32	0.83	2.11	
Antifungal	4.94	0.82	0.64	1.05		1.23	0.99	1.54	
Anxiety	7.55	0.99	0.82	1.20		0.99	0.81	1.20	
Arthritis	10.98	1.07	0.90	1.26		1.52	1.31	1.77	5.40
Asthma	8.54	1.46	1.20	1.77	3.78	1.83	1.52	2.21	6.62
Birth Control	7.98	0.95	0.81	1.11		0.85	0.72	1.00	15.00*
Blood Thinner	1.15	1.84	0.94	3.61		4.24	2.30	7.81	3.59
Bowel/Rectum	2.95	0.85	0.62	1.19		0.93	0.68	1.29	
Cold/Flu/Allergy	17.75	1.20	1.06	1.35	3.43	1.34	1.19	1.51	5.69
Depression	17.78	1.21	1.07	1.36	3.60	1.36	1.21	1.53	6.02
Diabetes	6.03	2.48	1.84	3.34	8.19	5.34	4.07	7.01	20.74
Edema	5.03	1.58	1.21	2.07	2.83	2.74	2.15	3.48	8.05
Eye Infection	11.87	1.13	0.98	1.33	1.52	1.30	1.12	1.50	3.44
Herpes	5.99	1.07	0.89	1.29	0.42	0.57	0.45	0.72	43.00*
High Blood Pressure	16.02	1.71	1.48	1.99	10.21	2.66	2.32	3.05	21.01
Inflammation	4.51	1.32	1.02	1.73	1.42	1.40	1.08	1.83	1.77
Insomnia	3.99	1.05	0.82	1.36		1.01	0.78	1.32	
Muscle Spasms	4.31	1.40	1.06	1.85	1.69	1.83	1.40	2.41	3.45
Nausea/Vomiting	4.86	1.24	0.95	1.61		1.62	1.27	2.08	2.93
Opioids	16.79	1.18	1.03	1.35	2.93	1.61	1.42	1.82	9.29
Osteoporosis	1.08	0.94	0.60	1.50		0.50	0.29	0.89	50.00*
Pain – non opioid	2.15	1.08	0.71	1.61		1.65	1.14	2.39	1.38
Skin	6.86	0.91	0.74	1.12		0.97	0.79	1.19	
Statins	11.93	2.32	1.94	2.78	13.61	2.84	2.39	3.37	18.00
Stomach Acid	1.17	1.14	0.65	1.99		2.02	1.23	3.31	1.18
Teeth/Gums	0.43	1.80	0.73	4.44		1.40	0.53	3.67	
Thyroid	12.79	1.09	0.96	1.25		1.23	1.08	1.40	2.86
Ulcers	9.33	1.30	1.09	1.55	2.72	1.52	1.28	1.80	4.63
Urinary Tract Infection	3.23	0.98	0.73	1.31		1.14	0.86	1.51	
Vitamins/Minerals	2.98	0.84	0.54	1.31		1.49	1.01	2.19	1.44

Note: Risk ratios and confidence intervals adjusted for age, sex, and year.

*Preventive Fraction.

Table 4. Total Annual Cost for Selected Medications According to Weight Classification

	Normal	Overweight	Obese		Normal	Overweight	Obese
Medication	Mean	Mean	Mean	Medication	Mean	Mean	Mean
Acid Reflux	3.51	15.84	14.94	High Blood Pressure	11.5	40.0	55.4
p value	0.0029	0.3115	.	p value	<.0001	0.013	.
Antibiotic	12.20	15.34	13.09	Inflammation	8.25	13.61	5.66
p value	0.8280	0.5933	.	p value	0.4421	0.0210	.
Anticonvulsants	8.82	5.63	20.01	Insomnia	2.7	4.6	2.8
p value	0.0198	0.0034	.	p value	0.9644	0.3237	.
Antifungal	0.74	2.11	2.22	Muscle Spasms	0.1	0.4	3.9
p value	0.0628	0.8977	.	p value	0.0025	0.0172	.
Anxiety	1.2	1.6	1.1	Nausea/Vomiting	0.2	1.1	1.0
p value	0.7948	0.1226	.	p value	0.007	0.6432	0
Arthritis	139.2	126.4	125.2	Opioids	2.6	7.4	9.5
p value	0.7593	0.9788	.	p value	<0.0001	0.1618	.
Asthma	32.0	38.4	46.5	Osteoporosis	5.1	2.9	0.3
p value	0.0256	0.2263	.	p value	0.0505	0.2597	.
Birth Control	39.1	32.1	25.8	Pain – Non Opioid	3.16	2.03	0.38
p value	0.0005	0.1049	.	p value	0.1552	0.3440	.
Blood Thinner	8.03	14.90	12.23	Skin	6.08	4.69	4.91
p value	0.6338	0.7675	.	p value	0.3537	0.8636	.
Bowels/Rectum	21.6	25.1	20.8	Statins	7.9	23.9	31.2
p value	0.9168	0.5598	.	p value	<.0001	0.1066	.
Cold/Flu/Allergy	13.9	21.1	17.5	Stomach Infection	2.61	1.88	2.25
p value	0.1763	0.1818	.	p value	0.7248	0.4936	.
Depression	31.2	53.7	57.5	Teeth/Gums	0.04	0.04	0.02
p value	0.0009	0.6405	.	p value	0.4433	0.4458	.
Diabetes	24.1	55.5	130.7	Thyroid	5.9	7.6	10.1
p value	<.0001	<.0001	.	p value	0.0003	0.0356	.
Edema	0.6	3.0	3.4	Ulcers	0.6	6.8	4.0
p value	0.0006	0.6529	.	p value	0.1366	0.3589	.
Eye Infection	4.4	4.8	4.2	Urinary Tract Infection	1.49	0.95	1.71
p value	0.7459	0.6384		p value	0.7002	0.1915	.
Herpes	14.43	15.02	7.63	Vitamins/Minerals	0.3	1.5	0.9
p value	0.0145	0.0094	.	p value	0.251	0.3174	.

Means adjusted for age, sex, and year.

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To what extent does sex, age, and BMI impact medical and pharmacy costs? A retrospective cohort study involving employees in a large school district

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To what extent does sex, age, and BMI impact medical and pharmacy costs? A retrospective cohort study involving employees in a large school district

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Objective To identify the extent that sex, age, and body mass index (BMI) is associated with medical and pharmacy costs.

Design Retrospective cohort.

Setting A school district in the Western United States involving 2531 workers continuously employed during 2011-2014.

Main outcome measures Medical and pharmacy costs and BMI.

Results Approximately 84% of employees participated in the wellness screening. Participants were 1.03 (95% CI 1.01- 1.06) times more likely to be women and younger (M = 47.8 vs. 49.8, p < 0.001). Median medical and pharmacy costs were higher for women than men, increased with age, and were greater in morbidly obese individuals (p < 0.001). Annual pharmacy claims were 18% more likely to be filed by women than men, 23% more likely filed by those aged ≥60 versus <40 years, and 6% more likely filed by morbidly obese individuals than of normal weight (p < 0.001) individuals. Greater medical and pharmacy costs in older age were most pronounced in underweight and morbidly obese groups. Higher use of medication among women than men was primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Higher medication use in older age was primarily related to medications used to treat gastrointestinal problems. Medication use was positively associated with BMI weight classifications for most of the 32 drug types considered, with exceptions involving birth control, herpes, and osteoporosis. A J-shape relationship was observed between BMI and medication use for acne, antibiotic, cold/influenza/allergy, eye infection, edema, muscle spasms, pain, and ulcers.

Conclusions Lowering medical and pharmacy costs requires weight management in older ages, particularly for underweight and obese men and women. Medical costs were significantly

reduced, likely due to effective drug treatment and prevention. Higher pharmacy costs for certain drugs among underweight individuals may be associated with poorer nutrition.

Strengths and limitations of this study

- A large cohort of employees was available for retrospective assessment of the association between sex, age, and BMI with medical and pharmacy costs.
- The association between sex, age, and 32 specific types of medication were assessed, some of which have not been previously considered.
- All active employees received employer-sponsored medical and pharmacy coverage, and above 84% had information that allowed us to determine body mass.
- A few medications may have contributed to weight gain, which we were unable to adjust for in the current study.
- The study population and patterns of prescription drug use may limit generalization of the results.

Introduction

Many companies offer wellness-screening programs consisting of health risk assessment and biometric screening. The 2016 Employer Health Benefits Survey found that among large firms (200 or more employees) in the United States, 59% offered health risk assessment (of which 32% had an incentive component) and 53% offered biometric screening (of which 31% included an incentive component).[1] These programs are intended to promote a greater sense of personal responsibility for lifestyle choices, identify the need for health behavior change, reduce future health problems, encourage patient management of existing health problems, decrease worker absenteeism, and improve job satisfaction and worker productivity.[2-7] Larger companies are also required to offer employer-sponsored medical and pharmacy coverage for their employees. Hence, information obtained on the health risk assessment and screenings can be compared with the medical and pharmacy costs.

Medical and pharmacy costs are influenced by a number of factors, including sex, age, and Body Mass Index (BMI).[8-10] Although medical costs are often a response to acute and chronic health conditions, pharmaceutical costs are often used to prevent more serious health problems. For example, antihypertensive medication, or statins, are useful in preventing cardiovascular disease;[11-13] multivitamins or folic acid for preventing congenital abnormalities;[14] aspirin and non-steroidal anti-inflammatory for preventing colorectal cancer;[15] bronchodilators, steroids, and anti-inflammatories for managing asthma;[16] and nonsteroidal anti-inflammatory drugs, steroids, analgesics, and immunosuppressive drugs for managing arthritis.[17] Consequently, wellness screening may actually increase use of prescription medication.[18]

Although a person's body weight may be associated with increased risk for various chronic health conditions and poorer health-related quality of life,[19 20] only in the last 15 years or so has its impact on healthcare expenditures been assessed.[10] Further, only a small number of studies have explored the association between body weight and prescription drug use. A study conducted in England found that overweight and obese individuals were more likely to receive medication for the cardiovascular system; gastrointestinal system; respiratory system; central nervous system; endocrine system; gynecology/urinary disorders; musculoskeletal and joint disorders; infections; eye, ear and oropharynx problems; and skin disorders.[21] A study in Sweden showed that use and cost of medication in general are significantly greater in obese individuals.[22] A study in the United States found that obesity was responsible for $7 billion in Medicare prescription drug costs in 2006.[23] Another study conducted in the United States identified increased medication use during 1988 through 2012, with the increase most prominent among obese individuals.[24] A large cross-sectional study of 9789 adults in the National Health and Nutrition Examination Survey (NHANES) found that obese individuals utilize several prescription drugs (e.g., hypertension, lipid-lowering, and diabetes medications) more frequently than normal weight individuals.[25] Another study based on NHANES data found that while medication use increased over time for obese individuals compared with normal weight individuals ages 40 years and older, the increase was only marginal for those aged 25-39 years.[26] One study found that obese individuals used more analgesic, asthma, cardiovascular, diabetes, intranasal allergic rhinitis, thyroid, and ulcer medications.[27]

The purpose of the current study was to identify the extent to which sex, age, and BMI weight classifications are associated with medical and pharmacy costs among a large group of teachers, administrators, and other school staff. These associations are also evaluated for 32 more

commonly prescribed medications.[28] Although studies have previously looked at the association between BMI and prescription medications, we evaluated some drugs that have not been formerly considered, and the breadth of drugs covered is greater than in past studies. In addition, evaluating the effect of being underweight on medical and pharmacy costs, and on specific drug types, is unique to this study.

Methods

Patient and Public Involvement

A retrospective cohort study was conducted that associated sex, age, and BMI with medical and pharmacy cost data for employees of a large school district in the western United States. Specific patients and or the general public was not involved in this study. Body mass index was obtained from those employees who participated in wellness screening. Employer-sponsored insurance was available to all employees. The school district comprised six high schools, eight junior high schools, and 31 elementary schools. Employees consisted of approximately three teachers to every one staff member (cooks, bus drivers, grounds keepers, maintenance workers, administrators, clerical workers, etc.). We were not provided specific job type and salary for each employee. However, we can assume that the teachers, administrators, counselors, and nurses, who represent almost all of the employees, had at least a college degree, that their salaries are commensurate with other school districts, and that the employer-sponsored insurance coverage was not strongly impacted by the employee's income or education.

The study involved the academic years 2010-11, 2011-12, 2012-13, and 2013-14. Employees were offered wellness screenings (personal health risk assessment [HRA] and biometric evaluation) each fall. Medical and pharmacy claims data were also obtained for the

employees in each academic year. Wellness screening and claims data were combined with a file of eligible employees and assessed within each academic year. The eligibility file contained information on current employment, sex, age, and year.

Wellness Screening

All employees were offered wellness screening. Although participation was voluntary, it was promoted through incentives. The HRA involved 36 questions. Biometric screenings involved measurements of body mass index (BMI kg/m^2), blood pressure (mm Hg), cholesterol (mg/dL), and glucose (mg/dL). The HRA and biometric screenings were provided at no cost to the employees, and were made available on location or with a personal physician. A health nurse or physician assisted the employee in interpreting their HRA and screening results, in order to help guide their need for lifestyle changes and control measures. The current study only considers BMI. Weight classifications are based on commonly accepted ranges of BMI, as follows: underweight (BMI < 18.5), normal weight (BMI 18.5-24), overweight (BMI 25-29), obese (BMI 30-39), and morbidly obese (BMI 40+).

Medical and Pharmacy Claims Data

All active employees received employer-sponsored medical and pharmacy coverage, for themselves and their families. The school district is fully insured with a retained-retention agreement that makes the plan act very much like a self-funded health plan. Each month the district pays a health insurance premium for the cost of healthcare and a small premium for reinsurance of catastrophic claims. Catastrophic claims greater than $250,000 are reinsured by a stop loss policy and are not paid for by the school district. Employee pharmacy data do not

include over-the-counter drugs, but only those medications requiring a prescription. In the United States, a drug is sold over-the-counter if the Food and Drug Administration deems it as sufficiently safe and effective. These medications are not included in the current study. Further, medical and pharmacy cost represents the amount paid by the insurance company as well as copays by the employee.

Statistical Techniques

Counts, means, standard deviations, medians, and percentages were used to describe the study population. Pair-wise comparisons of means were evaluated for statistical significance using the Student-Newman-Keuls Test. Risk ratios compare having a medical and pharmacy cost above the 50th percentile (vs. below), 75th percentile (vs. below), and 90th percentile (vs. below). Statistical significance was determined by the corresponding 95% confidence intervals. For selected medications, the risk of medication use was compared using risk ratios and attributable fraction percentages across the levels of sex, age, and BMI weight classifications. Statistical significance of differences in percent use of selected medications across sex, age, and BMI categories was based on two-sided tests of significance were based on the 0.05 level against a null hypothesis of no association. Data was evaluated using the statistical software package PC-SAS (version 9.4; SAS Institute, Inc., 2014).

Results

In 2010-11, there were 3023 eligible employees, of which 2531 (83.72%) remained employed through the academic year 2013-14. Those more likely to remain employed over the study period were 40-59 years of age and had lower medical and pharmacy costs (Table 1). In 2010-11, ages

ranged from 18-76, with mean age significantly younger for those who remained employed (46.9 vs. 49.2, p < 0.0001). Those who remained employed had significantly lower mean medical costs ($3056 vs. $7887, p < 0.0001) and mean pharmacy costs ($859 vs. $1105, p =0.0387). The results of this study are based on those continuously employed over the four academic years.

Most employees participated in annual wellness screening (84.1% in 2010-11, 84.4% in 2011-12, 87.6% in 2012-13, and 80.7% in 2013-14). In 2010-11, there was no significant difference in mean medical cost between those who participated in wellness screening and those who did not ($3148 vs. $2571, p = 0.2900). However, median medical cost was significantly greater for those who participated in wellness screening ($588 vs. $470, p = 0.0454). For all academic years, women were 1.03 (95% CI 1.01- 1.06) times more likely than men to complete annual wellness screenings, after adjusting for age and academic year. Participants in wellness screening were significantly younger (M = 47.8 vs. 49.8, p < 0.0001), after adjusting for sex and year. Those participating in wellness screening had significantly lower mean medical cost ($3093 vs. $4181, p = 0.0013), but experienced no significant difference in mean annual pharmacy costs, after adjusting for age, sex, and year.

Among participants in annual wellness screening, mean BMI remained constant across the academic years (Table 2). Mean BMI was greater for men than women and in ages 40 years and older. Medical and pharmacy costs were highly positively skewed, with considerable variability. Hence, identifying significant differences in the mean costs across the levels of sex, age, and year, were less likely to occur than to find significant differences in the median costs across the levels of these variables. Medical costs were higher for women than men, increased with age, and were greater in morbidly obese individuals. Pharmacy costs were higher in women than men, increased with age, and were lowest in those of normal weight.

The risk of medical and pharmacy costs above the 50th, 75th, and 90th percentiles are shown according to sex, age, and BMI weight classification in Table 3. Higher BMI has a greater impact on higher percentiles of medical and pharmacy costs. For example, morbidly obese compared with normal weight are 1.13 (13%), 1.30 (30%), and 1.93 (93%) more likely to have pharmacy costs above the 50th, 75th, and 90th percentiles, respectively. Medical and pharmacy costs above these percentiles are greater in women than men and increase with age.

Associations between selected percentiles of medical and pharmacy costs and BMI weight classifications varied according to age (Figure 1), but not sex (data not shown). Greater medical and pharmacy costs with older age groups are seen in the graph. However, the increasing costs with higher age are most pronounced in the underweight and morbidly obese groups.

Medication use is shown across sex, age, and BMI groups in Table 4. For any medication, women were 18% more likely to file a claim than men, employees 60 years of age or older were 23% more likely to file a claim than those less than 40 years, and morbidly obese were 6% more likely to file a claim than those of normal weight. For 22 of the 32 medications considered, the percentage of annual claims was higher for women than men. For only high blood pressure was the percentage of claims greater for men than women. For 24 of the medications, the percentage of annual claims increased with age. For 23 of the medications, the percentage of annual claims was associated with BMI (19 positively and 4 negatively). The strongest positive associations involved diabetes, high cholesterol (statins), high blood pressure, and edema. Negative associations involved acne, birth control, Herpes, and osteoporosis. The highest annual percent of acne, antibiotic, cold/influenza/allergy, and eye infection medications occurred in underweight individuals. For edema, muscle spasms, pain, and ulcers, medication use was comparatively high in underweight individuals, dropped for normal weight, and then increased in higher weight classifications.

We also report the attributable fraction in the population. For example, this statistic says that 8.82% of diabetes medication is attributed to being overweight, 20.34% is attributed to being obese, and 30.43% is attributed to being morbidly obese. Where the risk ratio is less than 1, the preventive fraction can be estimated. For example, the risk of requiring osteoporosis medication is lower for obese compared with normal weight employees (i.e., Risk Ratio = 0.54). The corresponding preventive fraction is 66%, meaning in the absence of obesity there would be 66% fewer claims for osteoporosis medication. The attributable fraction in the population and the preventive fraction both assume a cause-and-effect association between exposure and disease.

Discussion

The current study identified the degree to which sex, age, and BMI are associated with medical and pharmacy costs among employees in a large school district. Associations were also evaluated for 32 commonly prescribed medications.[28] The study extends previous research by including certain medications not previously evaluated and considering associations for all BMI weight classifications.

Higher medical and pharmacy costs among women, in older age, and among those not of normal weight is consistent with previous research.[8-10] Greater medical and pharmacy costs with older age are most pronounced in the underweight and morbidly obese groups. Hence, weight management at older ages appears particularly important in terms of lowering medical and pharmacy costs.

Higher medication use in women than men was primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Prescription costs for vitamins/minerals were also noticeably higher in women than men. Family planning and prenatal care may explain the greater use of birth control medications and vitamins/minerals among women. Loss of estrogen in women at older ages and female reproductive hormones may contribute to the higher level of osteoporosis and thyroid disease in women.[29 30]

Medication use was higher in those aged 60 years and older compared with those younger than 40, primarily because of diabetes, edema, high blood pressure, high cholesterol (statins), and thyroid disease. Previous research has shown that the risk of these diseases increase with age.[31-35] Medication use also noticeably increased with age for acid reflux, bowel/rectum, inflammation, and stomach acid. This is consistent with older age tending to be associated with more gastrointestinal problems.[36]

Medication use was highest in those who were morbidly obese. We found positive associations between body weight and higher use of medications for treating acid reflux, fungus, bacterial infections, arthritis, asthma, colds, influenza, allergies, depression, diabetes, edema, high blood pressure, muscle spasms, nausea/vomiting, pain, high cholesterol, stomach acid, thyroid, and ulcers. Other studies have identified a similar associations.[21 24 25 27] Morbidly obese individuals were also more likely to be prescribed vitamins and minerals than normal weight individuals. We did not find an association between body weight and increased use of medication for the bowel/rectum, skin, or urinary tract, which was counter to that found in other studies.[21 37-39] We also assessed but did not find a significant association for medications used to treat anxiety, insomnia, convulsions, or teeth and gums. The insignificant finding for anticonvulsants and teeth and gums may be because of insufficient power (i.e., small numbers).

Finally, we assessed the association between body weight and medications for birth control, herpes, and osteoporosis, wherein significant negative associations were found. We are not aware of other studies that have looked at the association between body weight and medications used for colds, influenza, depression, edema, birth control, herpes, or osteoporosis.

Greater use of medication to treat acid reflux or stomach acid among individuals with higher BMI is consistent with previous research showing hospitalization rates for reflux disease to be positively associated with BMI.[40 41] Another study found that higher BMI was associated with increased gastroesophageal reflux in both normal and overweight individuals.[42] Heavier body weight can add pressure to the stomach and diaphragm, thereby resulting in reflux. Further, increased use of medication for nausea/vomiting among individuals with higher BMI weight classifications is consistent with other research.[43]

The positive association between higher BMI and increased use of medication for ulcers is consistent with other research, particularly peptic (gastric and duodenal) ulcers.[44 45] The mechanism to explain the association between obesity and peptic ulcer disease remains unclear. Obesity is also associated with Helicobacter pylori, which has been linked with gastric ulcers.[46]

Previous research has shown that overweight and obese individuals are at greater risk for infections.[37-49] This is consistent with our findings that show increased use of antibiotics and medication for acne, colds/influenza/allergy, and eye infections among obese individuals. However, it has been shown previously that antibiotics can also weaken the immune system,[50] as well as lead to obesity.[51] Some inflammatory diseases known to be associated with obesity in which we found a positive association between obesity and medication included influenza,[52 53] heart disease,[54] diabetes,[55] allergies,[56-59] asthma,[60] edema,[61-63] and arthritis.[64-67] A compromised immune system may also trigger autoimmune diseases, including rheumatoid arthritis and thyroid disease,[68] as indicated in the current study.

Overweight and obese individuals were more likely to receive cold, influenza, or allergy medication. Obesity is associated with impaired immune response to influenza vaccination in humans.[69] Because vaccination is less successful for obese individuals,[70 71] a greater level of medication may be sought for treating colds, influenza, and allergies.

Overweight and obese individuals received higher levels of pain medication. Research indicates that the nature of the relationship between higher BMI and pain is likely indirect.[72] For example, greater body weight is associated with osteoarthritis, which, in turn, leads to pain.[73] Being overweight or obese may result in greater risk for back pain, joint pain, and muscle spasms.[74] One study also found that obese individuals were more sensitive than those of normal weight to pressure pain.[75]

We found that higher BMI was associated with depression medication, as consistent with previous research.[76-79] In one study, the age-adjusted level of depression among adults (ages 20 and older) in the United States was 43.2% for those with depression compared with 33.0% for those without depression.[80] It may be that higher use of prescription medication for depression among those with greater BMI is partly because these people are more likely to experience other conditions related to depression, such as heart disease and diabetes.[81-83]

There was more use of vitamins/minerals among morbidly obese employees. Of the prescribed vitamins/minerals only 8.0% involved vitamin B and 57.3% involved vitamin D. A previous study showed an association between low vitamin B12 and being obese.[84] Another study found that the prevalence of vitamin D deficiency was 35% greater in obese individuals.[85]

Acne, antibiotic, cold/influenza/allergy, and eye infection medications were prescribed more often for underweight individuals. This is consistent with underweight individuals having poorer nutrition and, consequently, a weakened immune system.[86] For edema, muscle spasms, pain, and ulcers, medication use showed a J-shape relationship with BMI weight classification. Poor nutrition may also explain the higher levels of medication use among underweight individuals for these medications. Despite mean medical costs being similar for those who participated in wellness screening during the first year of the study, over the four academic years, participants in wellness screening ended up having significantly lower mean medical costs. However, pharmacy costs did not go down. It has been shown that wellness screening can cause the number and cost of pharmaceuticals to go up, at least initially, as the need for treatment is identified.[87] Identified treatment needs can then, in turn, help prevent more costly health problems in the future. For example, medications used to treat high blood pressure can result in lowering the risk of diabetes, heart disease, stroke and kidney disease; treatment of insomnia can help lower the risk of irritability, depression or anxiety, difficulty paying attention, and accidents due to increased errors; treatment of high cholesterol with statins can help lower the risk of cardiovascular disease; treatment of oral infections can help reduce the risk of diabetes, cardiovascular disease, and preterm birth; and vitamins/minerals can help prevent a host of diseases (scurvy, rickets, anemia, neural tube defects, pellagra, etc.). High blood pressure and statin medications were among the highest prescribed in our study.

A limitation of this study involves external validity (generalizability). Specifically, the study considered those individuals who remained employed over all four academic years. These individuals were generally healthier. The study also focused on those who completed wellness screening because they contained BMI information. These employees were more likely women and younger. In addition, the causal direction between medication use and BMI could not be determined. That is, some medications may have contributed to body mass whereas others were in response to body mass. Finally, the current study did not have information on the use of vitamins or minerals obtained over the counter and small numbers made it impossible to evaluate the relationship between specific types of vitamins/minerals and sex, age, and BMI.

Conclusion

Weight management at older ages, particularly in underweight and morbidly obese individuals, is most important for lowering medical and pharmacy costs. Medical costs decreased, possibly because of effective drug treatment and prevention. Pharmacy costs remained constant, possibly because screening identified a need for certain medications. Greater use of medication among women than men is primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Greater medication use in older age is primarily related to medications used to treat gastrointestinal problems. Medication use was positively associated with BMI for most of the conditions being treated, with exceptions involving birth control, herpes, and osteoporosis. A J-shape relationship between BMI weight classification and medication use for acne, antibiotic, cold/influenza/allergy, eye infection, edema, muscle spasms, pain, and ulcers may be because of poorer nutrition in underweight individuals.

References

1. 2016 Employer Health Benefits Survey. kff.org. http://www.kff.org/health-costs/report/2016-employer-health-benefits-survey/. Published September 14, 2016. Accessed February 21, 2018.

2. Chen L, Hannon PA, Laing SS, Kohn MJ, Clark K, Pritchard S, Harris JR. Perceived workplace health support is associated with employee productivity. Am J Health Promot. 2015;29(3):139-146.

3. Centers for Disease Control and Prevention. cdc.gov. http://www.cdc.gov/sustainability/worksitewellness/ Worksite wellness. Updated December 9, 2014. Accessed March 18, 2018.

4. Michaels CN, Greene AM. Worksite wellness: increasing adoption of workplace health promotion programs. Health Promot Pract. 2013;14(4):473-479.

5. Witt LB, Olsen D, Ablah E. Motivating factors for small and midsized businesses to implement worksite health promotion. Health Promot Pract. 2013;14(6), 876-884.

6. Niessen MA, Kraaijenhagen RA, Dijkgraaf MG, van Pelt D, van Kalken CK, Peek N. Impact of a Web-based worksite health promotion program on absenteeism. J Occup Environ Med. 2012;54(4):404-408.

7. Kaspin LC, Gorman KM, Miller RM. Systematic review of employer-sponsored wellness strategies and their economic and health-related outcomes. Popul Health Manag. 2013;16(1): 14-21.

8. Metge C, Black C, Peterson S, Kozyrskyi AL. The population’s use of pharmaceuticals. Med Care. 1999;37(6 Suppl):JS42-JS59.

9. Bertakis K, Azari R, Helms L, Callahan E, Robbins J. Gender differences in the utilization of health care services. J Fam Pract. 2000;49(2):147-152.

10. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Int J Obes. 2005;29(3):334-339.

11. Karmali KN, Lloyd-Jones DM, Berendsen M, et al. Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. JAMA Cardiol. 2016;1(3):341-349.

12. Fretheim A, Odgaard-Jensen, Brørs O, Madsen S, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.

13. Taylor F, Huffman MD, Macedo A, et al. Statins for the primary prevention of cardiovascular disease. Cochrane. 2013. http://www.cochrane.org/CD004816/VASC_statins-primary-prevention-cardiovascular-disease. Accessed February 21, 2018.

14. Czeizel AE. Birth defects are preventable. Int J Med Sci. 2005;2(3):91-92.

15. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029-2043.

16. Asthma. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660. Published March 9, 2018. Accessed February 24, 2018.

17. Arthritis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/arthritis/diagnosis-treatment/drc-20350777. Published March 7, 2018. Accessed February 24, 2018.

18. Preventive Medicine Reports Paper

19. Thompson D, Edelsberg J, Colditz GA, Bird AP, Oster G. Lifetime health and economic consequences of obesity. Arch Intern Med. 1999;11;159(18):2177-2183.

20. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009;121(6):21-33.

21. Kinge JM, Morris S. Association between obesity and prescribed medication use in England. Econ Hum Biol. 2014;15:47-55.

22. Narbro K, Agren G, Jonsson E, et al. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. Arch Intern Med. 2002;162(18):2061-2069.

23. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff. 2009;28(5):w822-31.

24. Randhawa AK, Parikh JS, Kuk JL. Trends in medication use by body mass index and age between 1988 and 2012 in the United States. PLoS One. 2017 Sep 20;12(9):e0184089.

25. Kit BK, Ogden CL, Flegal KM. Prescription medication use among normal weight, overweight, and obese adults, United States, 2005-2008. Ann Epidemiol. 2012;22(2):112-119.

26. Jarrett B, Bloch GJ, Bennett D, Bleazard B, Hedges D. The influence of body mass index, age and gender on current illness: a cross-sectional study. Int J Obes. 2010;34(3):429-436.

27. Raebel MA, Malone DC, Conner DA, Xu S, Porter JA, Lanty FA. Health services use and health care costs of obese and nonobese individuals. Arch Intern Med. 2004;164(19):2135-2140.

28. Fuentes AV, Pineda MD, Venkata KCN. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. Pharmacy (Basel). 2018;6(2):E43.

29. Alswat KA. Gender disparities in osteoporosis. Clin Med Res. 2017;9(5): 382–387.

30. Li H, Li J. Thyroid disorders in women. Minerva Med. 2015;106(2):109-114.

31. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650-2664.

32. Trayes KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. Am Fam Physician. 2013;88(2):102-110.

33. Mc Donald Posso AJ, Motta Borrel JA, Fontes F, Cruz Gonzalez CE, Pachón Burgos AA, Cumbrera Ortega A. High blood pressure in Panama: Prevalence, sociodemographic and biologic profile, treatment, and control (STROBE). Medicine (Baltimore). 2014;93(22): e101.

34. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984-1994. Circulation. 1997;96(1):37-43.

35. Gesing A. The thyroid gland and the process of aging. Thyroid Res. 2015;8(Suppl 1):A8.

36. A L D'Souza. Ageing and the gut. Postgrad Med J. 2007; 83(975):44–53.

37. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916.

38. Brown J, Wimpenny P, Maughan H. Skin problems in people with obesity. Nurs Stand. 2004;18(35):38-42.

39. Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. Urology. 2012;79(2):266-269.

40. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup

Study. First National Health and Nutrition Examination Survey. Ann Epidemiol. 1999;9(7):424-435.

41. Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Alim Pharmacol Ther. 2013;37(5):555-563.
42. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Association between body mass index and gastroesophageal reflux symptoms in both normal weight and overweight women. N Engl J Med. 2006;354(22):2340-2348.
43. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol 2004;99(9):1807-1814.
44. Boylan MR, Khalili H, Huang ES, Chan AT. Measures of adiposity are associated with increased risk of peptic ulcer. Clin Gastroenterol Hepatol. 2014 Oct;12(10):1688-1694.
45. Kim J, Kim KH, Lee BJ. Association of peptic ulcer disease with obesity, nutritional components, and blood parameters in the Korean population. PLoS One. 2017;12(8): e0183777.
46. Xu M, Liu L, Yuan B, Yin J, Lu Q. Association of obesity with Helicobacter pylori infection: A retrospective study. World J Gastroenterol 2017;23(15):2750-2756.
47. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006;6(7)438-446.
48. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes. 2013;37:333-340.
49. Lübbeke A, Zingg M, Hoffmeyer P, et al. Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthopaedica. 2016;87(2):132-138

50. Yang JH, Bhargava P, McCloskey D, Mao N, Palsson BO, Collins JJ. Antibiotic-induced changes to the host metabolic environment inhibit drug efficacy and alter immune function. Cell Host & Mocrobe. 2017;22(6):757-765.

51. Early G. Current Evidence regarding antibiotic exposure and childhood obesity: an integrative review. Ped Nurs. 2017;43(4):169-174.

52. Bandaru P, Rajkimar H, Napanveettil G. The impact of obesity on immune response to infection and vaccine: an insight into plausible mechanisms. Endocrinol Metab Synd 2013;2:2.

53. Kwong JC, Campitelli MA, Rosella LC. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada: a cohort study. Clin Infect Dis. 2011;53(5):413-421.

54. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010;2010:535918.

55. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.

56. Ciprandi G, Pistorio A, Tosca M, Ferraro MR, Cirillo I. Body mass index, respiratory function and bronchial hyperactivity in allergic rhinitis and asthma. Respir Med 2009;103(2):289-295.

57. Gorgievska-Sukarovska B, Lipozencić J, Susac A. Obesity and allergic diseases. Acta Dermatovenerol Croat. 2008;16(4):231-235.

58. Shah R, Yang Y. Health and economic burden of obesity in elderly individuals with asthma in the United States. Popul Health Manag 2015;18(3):186-191.

59. Guo Y, Moon JY, Laurie CC, et al. Genetic Predisposition to Obesity is associated with Asthma in US Hispanics/Latinos: Results from the Hispanic Community Health Study/Study of Latinos. Allergy. 2018;doi: 10.1111/all.13450. [Epub ahead of print]

60. Rodriguez D. Obesity and Asthma – What's the Connection. https://www.everydayhealth.com/asthma/obesity-connection.aspx. Published August 28, 2013. Accessed April 12, 2018.

61. Greene, A.K., et al. Lower-Extremity Lymphedema and Elevated Body-Mass Index. N Engl J Med. 2012;366:2136-2137.

62. Helyer, L.K., et al. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. Breast J. 2012;16(1):48-54.

63. Greene AK, Grant FD, Slavin SA, Maclellan RA. Obesity-induced lymphedema: clinical and lymphoscintigraphic features. Plast Reconstr Surg. 2015;135(6):1715-1719.

64. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138(2):185-193.

65. Baodong Qin, Min Yang, Haitao Fu, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17(1):86.

66. Feng J, Chen Q, Yu F, et al. Body mass index and risk of rheumatoid arthritis: a meta-analysis of observational studies. Medicine. 2016;95(8):e2859.

67. Albrecht K, Richter A, Callhoff J, et al. Body mass index distribution in rheumatoid arthritis: a collaborative analysis from three large German rheumatoid arthritis databases. Arthritis Res Ther. 2016;18:149.

68. Rodriguez D. How Your Immune System Worsens Arthritis. EverydayHealth.com. https://www.everydayhealth.com/arthritis/understanding/the-immune-system.aspx. Published August 1, 2012. Accessed April 11, 2018.

69. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes. 2012;36(8):1072-1077.

70. Painter SD, Ovsyannikoa IG, Poland GA. The weight of obesity on the human immune response to vaccination. Vaccine. 2015;33(36): 4422–4429.

71. Young KM, Gray CM, Bekker LG. Is Obesity a Risk Factor for Vaccine Non-Responsiveness? PLoS One**.** 2013;8(12): e82779.

72. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8:399-408.

73. Erdmann J. Osteoarthritis and Obesity. www.arthritis.org. https://www.arthritis.org/living-with-arthritis/comorbidities/obesity-arthritis/osteoarthritis-and-obesity.php. Accessed April 11, 2018.

74. American Obesity Association. Health effects of obesity. AOA Fact Sheets. 2002.

75. Tashani OA, Asitita R, Sharp D, Johnson MI. Body mass index and distribution of body fat can influence sensory detection and pain sensitivity. Eur J Pain 2017;21(7):1186-1196.

76. Rathee N. Obesity and depression: Are they related? Indian J Health Well. 2017;8(12):1472-1475.

77. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. Int J Obesity. 2009;33(2):257-266.

78. Onyike CU, Crum RM, Lee HB, Lyketsos DG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003;158(12):1139-1147.

79. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2008;70(3):288-297.

80. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005-2010. NCHS Data Brief, No. 167, October 2014.

81. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry 2004;65(5):634-651.

82. Ferraro KF, Su Y, Gretebeck RJ, Black DR, Badylak SF. Body mass index and disability in adulthood: A 20-year panel study. Am J Public Health. 2002;92(5):834-840.

83. Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. J Psychosom Res. 2002;53(4):859-863.

84. Baltaci D, Kutlucan A, Turker Y, et al. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Med Glas. 2013;10(2):203-210.

85. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341-349.

86. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? The Lancet 2003;361:2226-2234.

87. Merrill RM, Telford CT. Pharmaceutical use according to participation in worksite wellness screening and health campaigns. Prev Med Rep 2018;12:158-163.

Footnotes

Contributors: RMM conceived and designed the epidemiological study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. RPF interpreted the data, provided a literature review, and revised the manuscript. Both authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by both authors.

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Table 1 Characterization of the study group according to sex, age, medical and pharmacy costs

			Continuously Employed			
	No.	%	%	Chi-square p value	Risk Ratio	95% CI
Sex						
Men	797	26.36	84.69	0.3884	1.00	
Women	2226	73.64	83.38		0.98	0.95-1.02
Age Group						
18-39	770	25.47	82.21	< 0.0001	1.00	
40-49	806	26.66	89.45		1.09	1.05-1.13
50-59	1088	35.99	88.24		1.07	1.03-1.12
60-76	359	11.88	60.45		0.74	0.67-0.80
Medical Cost (USD)						
0-184	755	25.0	87.55	< 0.0001	1.00	
185-604	757	25.0	85.07		0.97	0.93-1.01
605-2049	755	25.0	84.64		0.97	0.93-1.01
2050-7191	454	15.0	79.30		0.91	0.86-0.96
7192+	302	10.0	75.17		0.86	0.80-0.92
Pharmacy Cost (USD)						
0-6	759	25.0	86.92	< 0.0001	1.00	
7-194	755	25.0	85.21		0.99	0.69-1.03
195-903	755	25.0	82.59		0.96	0.92-1.00
904-2303	452	15.0	84.14		0.99	0.94-1.04
2304+	302	10.0	74.92		0.86	0.80-0.93

Sex, age, medical and pharmacy costs apply to the 2010-11 academic year.

Table 2 Medical and pharmacy costs according to sex, age, year, and body mass index

	BMI (kg/m^2)			Medical Cost (USD)				Median one-way analysis	Pharmacy Cost (USD)				Median one-way analysis
	Mean	SD	SNK	Mean	SD	SNK	Median	p value	Mean	SD	SNK	Median	p value
Sex													
Men	29.35	5.80	A	2869	10581	A	373	< 0.0001	725	2324	A	53	< 0.0001
Women	27.26	6.47	B	3447	12049	A	741		963	3550	B	238	
Age Group													
18-39	27.17	6.06	A	2236	9344	A	389	< 0.0001	660	3342	A	70	< 0.0001
40-49	27.76	6.42	B	3052	12366	B	503		750	2806	A	106	
50-59	28.05	6.55	B	3935	12579	B	845		1021	3288	B	261	
60-76	28.17	6.13	B	3749	10831	B	989		1288	3990	C	344	
Year													
2010-11	27.89	6.40	A	3188	10524	A	605	0.2313	830	2247	A	195	0.0016
2011-12	27.79	6.31	A	3621	12816	A	610		953	3180	A	189	
2012-13	27.87	6.59	A	3208	11836	A	670		934	3571	A	173	
2013-14	27.63	6.16	A	3191	11557	A	651		894	3913	A	141	
BMI (kg/m^2)													
Underweight				2191	1190	A	647	0.0003	1454	6706	A	224	0.0004
Normal weight				2826	333	A	650		779	3285	B	167	
Overweight				3174	514	A	603		926	3085	A, B	169	
Obese				3544	459	A	665		1031	3458	A, B	228	
Morbidly obese				6911	2092	B	1033		853	1493	A, B	242	

SNK: Student-Newman-Keuls Test. Different letters indicate significant difference at the 0.05 level.

Table 3 Risk of medical and pharmacy costs (USD) above the 50th, 75th, and 90th percentiles according to BMI weight classification, sex, and age

	Medical						Pharmacy					
	50th percentile Above vs. below		75th percentile Above vs. below		90th percentile Above vs. below		50th percentile Above vs. below		75th percentile Above vs. below		90th percentile Above vs. below	
	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI
Sex												
Men	1.00		1.00		1.00		1.00		1.00		1.00	
Women	1.43	1.36-1.51	1.47	1.35-1.60	1.42	1.24-1.64	1.58	1.50-1.66	1.59	1.46-1.74	1.14	1.00-1.29
Age Groups												
18-39	1.00		1.00		1.00		1.00		1.00		1.00	
40-49	1.16	1.08-1.23	1.15	1.03-1.29	1.08	0.90-1.28	1.14	1.07-1.22	1.45	1.29-1.64	1.72	1.37-2.15
50-59	1.50	1.42-1.59	1.65	1.50-1.82	1.36	1.16-1.58	1.48	1.39-1.56	2.28	2.05-2.55	2.82	2.30-3.46
60+	1.61	1.52-1.72	1.83	1.64-2.04	1.33	1.11-1.60	1.57	1.48-1.68	2.57	2.29-2.89	3.78	3.06-4.68
BMI (kg/m^2)												
Underweight	1.05	0.88-1.26	0.91	0.64-1.31	0.61	0.28-1.35	2.05	1.25-3.34	1.05	0.74-1.48	2.05	1.25-3.34
Normal weight	1.00		1.00		1.00		1.00		1.00		1.00	
Overweight	0.95	0.90-1.00	0.95	0.86-1.05	1.01	0.85-1.20	1.01	0.95-1.06	1.18	1.07-1.30	1.68	1.41-2.00
Obese	1.00	0.95-1.06	1.14	1.03-1.25	1.21	1.01-1.43	1.11	1.05-1.17	1.19	1.08-1.31	1.76	1.47-2.12
Morbidly obese	1.18	1.08-1.29	1.62	1.40-1.87	2.18	1.72-2.77	1.13	1.03-1.25	1.30	1.09-1.55	1.93	1.43-2.61

Shaded cells represent statistical significance at the 0.05 level.

Table 4 Medication use according to sex, age, and BMI weight classification

		Sex		Age Group				Body Mass Index (kg/m²)				
		Men	Women	18-39	40-49	50-59	60+	Underweight	Normal weight	Over weight	Obese	Morbidly obese
Medication	%											
Acid Reflux	5.75	5.56	5.81	3.02	4.54	7.14	8.36	3.57	4.34	5.36	7.19	9.14
Risk ratio		1.00	1.04	1.00	1.50	2.36	2.77	0.82	1.00	1.24	1.66	2.11
AF_p (%)		0.00	0.26	0.00	2.81	7.27	9.23		0.00	1.33	3.64	5.98
Acne	7.17	3.15	8.62	7.15	7.03	7.16	7.40	9.82	8.81	6.64	6.34	6.18
Risk ratio		1.00	2.74	1.00	0.98	1.00	1.03	1.11	1.00	0.75	0.72	0.70
AF_p (%)		0.00	11.07	0.00		0.01	0.25	0.82	0.00			
Antibiotic	21.21	17.81	22.44	18.72	20.76	22.76	21.93	25.89	20.54	20.74	23.73	21.24
Risk ratio		1.00	1.26	1.00	1.11	1.22	1.17	1.26	1.00	1.01	1.16	1.03
AF_p (%)		0.00	5.23	0.00	2.26	4.38	3.51	5.24	0.00	0.21	3.19	0.72
Anticonvulsants	1.49	1.39	1.53	1.84	1.32	1.45	1.40	2.68	1.25	1.13	1.65	1.61
Risk ratio		1.00	1.10	1.00	0.72	0.79	0.76	2.14	1.00	0.90	1.32	1.29
AF_p (%)		0.00	0.15	0.00				1.68	0.00		0.47	0.43
Antifungal	5.29	2.61	5.81	5.64	6.03	4.24	3.87	5.36	5.83	3.81	6.24	6.18
Risk ratio		1.00	2.23	1.00	1.07	0.75	0.69	0.92	1.00	0.65	1.07	1.06
AF_p (%)		0.00	6.09	0.00	0.36				0.00		0.37	0.32
Anxiety	7.88	6.31	8.45	6.42	7.80	8.36	8.97	8.93	7.22	7.11	7.29	6.45
Risk ratio		1.00	1.34	1.00	1.21	1.30	1.40	1.24	1.00	0.98	1.01	0.89
AF_p (%)		0.00	2.60	0.00	1.67	2.33	3.03	1.83	0.00		0.08	
Arthritis	11.06	11.13	11.03	7.72	10.53	12.83	12.56	7.14	9.36	10.72	13.84	14.78
Risk ratio		1.00	0.99	1.00	1.36	1.66	1.63	0.76	1.00	1.15	1.48	1.58
AF_p (%)		0.00		0.00	3.87	6.82	6.48		0.00	1.58	5.03	6.02
Asthma	8.61	7.19	9.13	7.48	8.80	8.00	11.22	6.25	6.24	8.74	10.39	10.75

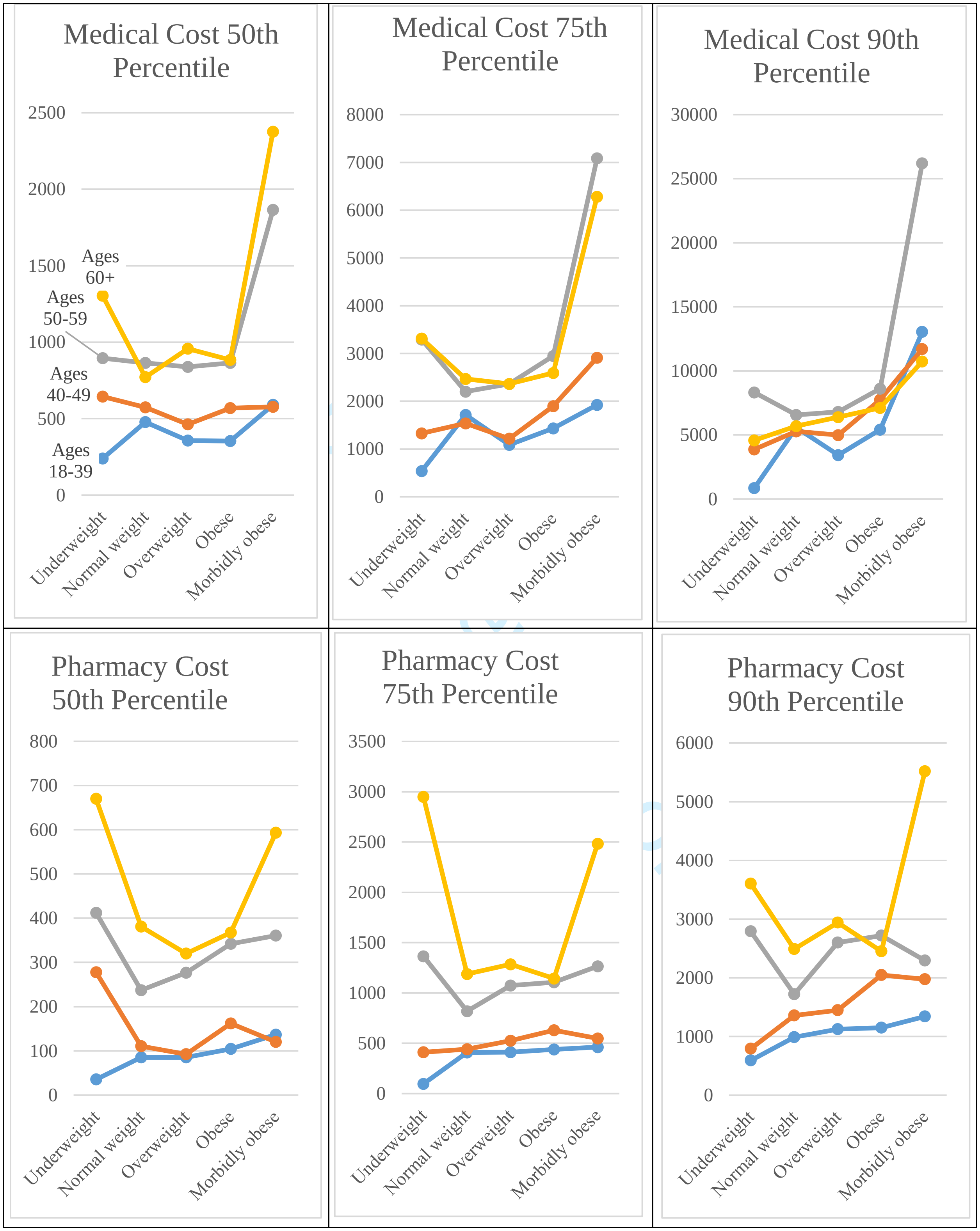
Risk ratio		1.00	1.27	1.00	1.18	1.07	1.50	1.00	1.00	1.40	1.67	1.72
AF$_p$ (%)		0.00	2.27	0.00	1.50	0.59	4.13	0.01	0.00	3.33	5.42	5.86
Birth Control	8.71	0.24	10.88	21.13	8.77	2.59	0.95	10.71	11.69	7.30	6.34	6.99
Risk ratio		1.00	45.33	1.00	0.42	0.12	0.04	0.92	1.00	0.62	0.54	0.60
AF$_p$ (%)		0.00	79.43	0.00					0.00			
Bowel/Rectum	3.06	2.75	3.17	1.76	2.84	3.53	4.15	1.79	3.15	2.87	2.85	2.96
Risk ratio		1.00	1.15	1.00	1.61	2.01	2.36	0.57	1.00	0.91	0.90	0.94
AF$_p$ (%)		0.00	0.47	0.00	1.84	2.99	3.99		0.00			
Cold/Influenza/Allergy	17.80	14.52	18.99	15.73	18.30	18.14	19.07	22.32	15.53	18.56	20.38	22.04
Risk ratio		1.00	1.31	1.00	1.16	1.15	1.21	1.44	1.00	1.20	1.31	1.42
AF$_p$ (%)		0.00	5.20	0.00	2.83	2.65	3.64	7.22	0.00	3.36	5.27	6.94
Depression	18.24	10.28	21.14	12.51	19.30	20.75	18.84	15.18	16.20	17.59	20.83	18.55
Risk ratio		1.00	2.06	1.00	1.54	1.66	1.51	0.94	1.00	1.09	1.29	1.15
AF$_p$ (%)		0.00	16.16	0.00	9.01	10.73	8.45		0.00	1.54	4.95	2.58
Diabetes	6.32	6.48	6.22	2.53	4.50	7.82	10.94	1.79	2.24	5.67	11.29	17.74
Risk ratio		1.00	0.96	1.00	1.78	3.09	4.32	0.80	1.00	2.53	5.04	7.92
AF$_p$ (%)		0.00		0.00	4.69	11.67	17.36		0.00	8.82	20.34	30.43
Edema	5.14	3.12	5.87	2.04	3.64	6.48	8.86	6.25	3.08	4.66	7.29	12.90
Risk ratio		1.00	1.88	1.00	1.78	3.18	4.34	2.03	1.00	1.51	2.37	4.19
AF$_p$ (%)		0.00	4.33	0.00	3.88	10.06	14.66	5.02	0.00	2.57	6.56	14.08
Eye Infection	12.01	9.23	12.87	11.44	13.06	11.13	12.34	14.29	11.02	12.12	13.64	9.68
Risk ratio		1.00	1.39	1.00	1.14	0.97	1.08	1.30	1.00	1.10	1.24	0.88
AF$_p$ (%)		0.00	4.52	0.00	1.67		0.94	3.44	0.00	1.18	2.78	
Herpes	6.30	3.26	6.86	4.82	7.24	6.12	4.71	1.79	7.66	7.22	4.20	1.88
Risk ratio		1.00	2.10	1.00	1.50	1.27	0.98	0.23	1.00	0.94	0.55	0.25
AF$_p$ (%)		0.00	6.50	0.00	3.07	1.67			0.00			
High Blood Pressure	16.49	19.95	15.60	4.58	11.05	22.78	29.39	6.25	8.54	17.44	24.68	31.99
Risk ratio		1.00	0.78	1.00	2.41	4.97	6.42	0.73	1.00	2.04	2.89	3.75
AF$_p$ (%)		0.00		0.00	18.89	39.59	47.18		0.00	14.66	23.76	31.17
Inflammation	1.19	0.68	1.37	0.69	0.87	1.50	1.68	1.79	0.98	1.40	0.80	1.61
Risk ratio		1.00	2.01	1.00	1.26	2.17	2.43	1.83	1.00	1.43	0.82	1.64
AF$_p$ (%)		0.00	1.19	0.00	0.31	1.38	1.68	0.97	0.00	0.51		0.76

Insomnia	4.23	2.24	4.95	2.70	3.60	5.72	4.04	8.93	4.07	3.92	3.85	4.84
Risk ratio		1.00	2.21	1.00	1.33	2.12	1.50	2.19	1.00	0.96	0.95	1.19
AF_p (%)		0.00	4.87	0.00	1.39	4.52	2.06	4.81	0.00			0.79
Muscle Spasms	4.34	3.53	4.64	3.11	4.57	4.93	4.37	5.36	3.29	4.27	5.44	6.99
Risk ratio		1.00	1.31	1.00	1.47	1.59	1.41	1.63	1.00	1.30	1.65	2.12
AF_p (%)		0.00	1.35	0.00	2.00	2.48	1.73	2.66	0.00	1.28	2.76	4.65
Nausea/Vomiting	5.01	3.77	5.47	5.44	4.85	4.83	5.10	4.46	4.14	4.50	6.19	5.65
Risk ratio		1.00	1.45	1.00	0.89	0.89	0.94	1.08	1.00	1.09	1.50	1.36
AF_p (%)		0.00	2.21	0.00				0.39	0.00	0.43	2.42	1.79
Opioids	17.04	15.98	17.42	14.14	16.29	18.62	18.73	17.86	13.39	15.77	20.28	27.69
Risk ratio		1.00	1.09	1.00	1.15	1.32	1.32	1.33	1.00	1.18	1.51	2.07
AF_p (%)		0.00	1.51	0.00	2.53	5.12	5.24	5.38	0.00	2.94	8.06	15.40
Osteoporosis	1.21	0.07	1.63	0.00	0.17	1.30	4.37	0.89	1.56	1.20	0.85	0.00
Risk ratio		1.00	23.29	1.00				0.57	1.00	0.77	0.54	0.00
AF_p (%)		0.00	21.24	0.00					0.00			
Pain – non opioid	2.19	1.63	2.39	2.78	2.15	1.98	1.91	3.57	1.73	1.67	2.55	2.96
Risk ratio		1.00	1.47	1.00	0.77	0.71	0.69	2.06	1.00	0.97	1.47	1.71
AF_p (%)		0.00	1.01	0.00				2.28	0.00		1.03	1.53
Skin	6.84	4.88	7.55	5.44	6.44	7.37	8.24	6.25	7.25	6.41	7.19	5.38
Risk ratio		1.00	1.55	1.00	1.18	1.35	1.51	0.86	1.00	0.88	0.99	0.74
AF_p (%)		0.00	3.61	0.00	1.24	2.37	3.40		0.00			
Statins	12.05	15.91	10.65	1.76	7.07	16.46	24.51	2.68	5.59	15.15	17.18	21.77
Risk ratio		1.00	0.67	1.00	4.02	9.35	13.93	0.48	1.00	2.71	3.07	3.89
AF_p (%)		0.00		0.00	26.66	50.16	60.90		0.00	17.09	19.99	25.86
Stomach Acid	1.19	1.49	1.07	0.86	1.25	0.99	1.96	0.89	0.81	1.01	1.90	1.08
Risk ratio		1.00	0.72	1.00	1.45	1.15	2.28	1.10	1.00	1.25	2.35	1.33
AF_p (%)		0.00		0.00	0.54	0.18	1.50	0.12	0.00	0.29	1.58	0.40
Teeth/Gums	0.43	0.37	0.46	0.37	0.35	0.43	0.67	0.00	0.27	0.43	0.35	0.27
Risk ratio		1.00	1.24	1.00	0.95	1.16	1.81	0.00	1.00	1.59	1.30	1.00
AF_p (%)		0.00	0.10	0.00		0.07	0.35		0.00	0.25	0.13	0.00
Thyroid	12.76	2.99	16.31	4.37	11.19	16.92	17.61	6.25	13.97	12.74	13.94	19.09
Risk ratio		1.00	5.45	1.00	2.56	3.87	4.03	0.45	1.00	0.91	1.00	1.37

AF$_p$ (%)		0.00	36.24	0.00	16.61	26.82	27.88		0.00			4.47
Ulcers	9.38	8.55	9.69	8.30	8.28	10.19	10.88	10.71	7.59	9.90	10.99	15.32
Risk ratio		1.00	1.13	1.00	1.00	1.23	1.31	1.41	1.00	1.30	1.45	2.02
AF$_p$ (%)		0.00	1.24	0.00		2.09	2.83	3.71	0.00	2.78	4.03	8.72
Urinary Tract Infection	3.01	0.20	4.44	3.39	3.08	3.45	3.25	6.25	3.83	2.83	3.50	3.76
Risk ratio		1.00	22.20	1.00	0.91	1.02	0.96	1.63	1.00	0.74	0.91	0.98
AF$_p$ (%)		0.00	38.95	0.00		0.05		1.87	0.00			
Vitamins/Minerals	2.07	0.71	2.57	2.49	1.73	1.88	2.47	0.00	2.07	1.28	1.75	5.38
Risk ratio		1.00	3.62	1.00	0.69	0.76	0.99	0.00	1.00	0.62	0.85	2.60
AF$_p$ (%)		0.00	5.14	0.00					0.00			3.20
All prescriptions	80.87	71.40	84.32	71.52	78.45	85.24	88.00	83.93	81.46	81.28	83.47	86.29
Risk ratio		1.00	1.18	1.00	1.10	1.19	1.23	1.03	1.00	1.00	1.02	1.06
AF$_p$ (%)		0.00	12.77	0.00	7.27	13.43	15.71	2.39	0.00		1.96	4.58

AF$_p$: Attributable fraction in the population. Shaded cells represent statistical significance at the 0.05 level. Cells that are left blank had a negative AF$_p$. In these cases the preventive fraction ([Risk Ratio – 1] × 100) is more appropriate.

Figure 1. Median medical and pharmacy cost (USD) according to Body Mass Index weight classifications and age


Medical Cost 50th Percentile
2500
2000
1500
1000
500
0
Ages 60+
Ages 50-59
Ages 40-49
Ages 18-39
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Medical Cost 75th Percentile
8000
7000
6000
5000
4000
3000
2000
1000
0
Medical Cost 90th Percentile
30000
25000
20000
15000
10000
5000
0
Pharmacy Cost 50th Percentile
800
700
600
500
400
300
200
100
0
Pharmacy Cost 75th Percentile
3500
3000
2500
2000
1500
1000
500
0
Pharmacy Cost 90th Percentile
6000
5000
4000
3000
2000
1000
0

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page/line numbers
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1/6, 2/25
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Done
Objectives	3	State specific objectives, including any prespecified hypotheses	Done
Methods			
Study design	4	Present key elements of study design early in the paper	Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Done
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done
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	Done
Bias	9	Describe any efforts to address potential sources of bias	Done
Study size	10	Explain how the study size was arrived at	Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Done
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
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	Done
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Done
		(c) Summarise follow-up time (eg, average and total amount)	Done
Outcome data	15*	Report numbers of outcome events or summary measures over time	Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Done

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Done
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
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	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done
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	Done

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

BMJ Open

To what extent does sex, age, and BMI impact medical and pharmacy costs? A retrospective cohort study involving employees in a large school district

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Secondary Subject Heading:	Public health, Epidemiology
Keywords:	health risks, screening, prescription medication, health risk appraisal, body mass index, pharmaceutical costs

To what extent does sex, age, and BMI impact medical and pharmacy costs? A retrospective cohort study involving employees in a large school district

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Keywords: body mass index, obesity, prevention, pharmaceuticals, screening

Word count: 3527

Objective To identify the extent that sex, age, and body mass index (BMI) is associated with medical and pharmacy costs.

Design Retrospective cohort.

Setting A school district in the Western United States involving 2531 workers continuously employed during 2011-2014.

Main outcome measures Medical and pharmacy costs and BMI.

Results Approximately 84% of employees participated in the wellness screening. Participants were 1.03 (95% CI 1.01- 1.06) times more likely to be women and younger (M = 47.8 vs. 49.8, $p < 0.001$). Median medical and pharmacy costs were higher for women than men, increased with age, and were greater in morbidly obese individuals ($p < 0.001$). Annual pharmacy claims were 18% more likely to be filed by women than men, 23% more likely filed by those aged ≥60 versus <40 years, and 6% more likely filed by morbidly obese individuals than of normal weight ($p < 0.001$) individuals. Greater medical and pharmacy costs in older age were most pronounced in underweight and morbidly obese groups. Higher use of medication among women than men was primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Higher medication use in older age was primarily related to medications used to treat gastrointestinal problems. Medication use was positively associated with BMI weight classifications for most of the 33 drug types considered, with exceptions involving birth control, herpes, and osteoporosis. A J-shape relationship was observed between BMI and medication use for acne, antibiotic, cold/influenza/allergy, eye infection, edema, muscle spasms, pain, and ulcers.

Conclusions Lowering medical and pharmacy costs requires weight management in older ages, particularly for underweight and obese men and women. Medical costs were significantly

reduced, likely due to effective drug treatment and prevention. Higher pharmacy costs for certain drugs among underweight individuals may be associated with poorer nutrition.

Strengths and limitations of this study

- A large cohort of employees was available for retrospective assessment of the association between sex, age, and BMI with medical and pharmacy costs.
- The association between sex, age, and 33 specific types of medication were assessed, some of which have not been previously considered.
- All active employees received employer-sponsored medical and pharmacy coverage, and above 84% had information that allowed us to determine body mass.
- A few medications may have contributed to weight gain, which we were unable to adjust for in the current study.
- The study population and patterns of prescription drug use may limit generalization of the results.

Introduction

Many companies offer wellness-screening programs consisting of health risk assessment and biometric screening. The 2016 Employer Health Benefits Survey found that among large firms (200 or more employees) in the United States, 59% offered health risk assessment (of which 32% had an incentive component) and 53% offered biometric screening (of which 31% included an incentive component).[1] These programs are intended to promote a greater sense of personal responsibility for lifestyle choices, identify the need for health behavior change, reduce future health problems, encourage patient management of existing health problems, decrease worker absenteeism, and improve job satisfaction and worker productivity.[2-7] Larger companies are also required to offer employer-sponsored medical and pharmacy coverage for their employees. Hence, information obtained on the health risk assessment and screenings can be compared with the medical and pharmacy costs.

Medical and pharmacy costs are influenced by a number of factors, including sex, age, and Body Mass Index (BMI).[8-10] Although medical costs are often a response to acute and chronic health conditions, pharmaceutical costs are often used to prevent more serious health problems. For example, antihypertensive medication, or statins, are useful in preventing cardiovascular disease;[11-13] multivitamins or folic acid for preventing congenital abnormalities;[14] aspirin and non-steroidal anti-inflammatory for preventing colorectal cancer;[15] bronchodilators, steroids, and anti-inflammatories for managing asthma;[16] and nonsteroidal anti-inflammatory drugs, steroids, analgesics, and immunosuppressive drugs for managing arthritis.[17] Consequently, wellness screening may actually increase use of prescription medication.[18]

Although a person's body weight may be associated with increased risk for various chronic health conditions and poorer health-related quality of life,[19 20] only in the last 15 years or so has its impact on healthcare expenditures been assessed.[10] Further, only a small number of studies have explored the association between body weight and prescription drug use. A study conducted in England found that overweight and obese individuals were more likely to receive medication for the cardiovascular system; gastrointestinal system; respiratory system; central nervous system; endocrine system; gynecology/urinary disorders; musculoskeletal and joint disorders; infections; eye, ear and oropharynx problems; and skin disorders.[21] A study in Sweden showed that use and cost of medication in general are significantly greater in obese individuals.[22] A study in the United States found that obesity was responsible for $7 billion in Medicare prescription drug costs in 2006.[23] Another study conducted in the United States identified increased medication use during 1988 through 2012, with the increase most prominent among obese individuals.[24] A large cross-sectional study of 9789 adults in the National Health and Nutrition Examination Survey (NHANES) found that obese individuals utilize several prescription drugs (e.g., hypertension, lipid-lowering, and diabetes medications) more frequently than normal weight individuals.[25] Another study based on NHANES data found that while medication use increased over time for obese individuals compared with normal weight individuals ages 40 years and older, the increase was only marginal for those aged 25-39 years.[26] One study found that obese individuals used more analgesic, asthma, cardiovascular, diabetes, intranasal allergic rhinitis, thyroid, and ulcer medications.[27]

The purpose of the current study was to identify the extent to which sex, age, and BMI weight classifications are associated with medical and pharmacy costs among a large group of teachers, administrators, and other school staff. These associations are also evaluated for 33 more

commonly prescribed medications.[28] Although studies have previously looked at the association between BMI and prescription medications, we evaluated some drugs that have not been formerly considered, and the breadth of drugs covered is greater than in past studies. In addition, evaluating the effect of being underweight on medical and pharmacy costs, and on specific drug types, is unique to this study.

Methods

Patient and Public Involvement

A retrospective cohort study was conducted that associated sex, age, and BMI with medical and pharmacy cost data for employees of a large school district in the western United States. Specific patients and or the general public was not involved in this study. Body mass index was obtained from those employees who participated in wellness screening. Employer-sponsored insurance was available to all employees. The school district comprised six high schools, eight junior high schools, and 31 elementary schools. Employees consisted of approximately three teachers to every one staff member (cooks, bus drivers, grounds keepers, maintenance workers, administrators, clerical workers, etc.). We were not provided specific job type and salary for each employee. However, we can assume that the teachers, administrators, counselors, and nurses, who represent almost all of the employees, had at least a college degree, that their salaries are commensurate with other school districts, and that the employer-sponsored insurance coverage was not strongly impacted by the employee's income or education.

The study involved the academic years 2010-11, 2011-12, 2012-13, and 2013-14. Employees were offered wellness screenings (personal health risk assessment [HRA] and biometric evaluation) each fall. Medical and pharmacy claims data were also obtained for the

employees in each academic year. Wellness screening and claims data were combined with a file of eligible employees and assessed within each academic year. The eligibility file contained information on current employment, sex, age, and year.

Wellness Screening

All employees were offered wellness screening. Although participation was voluntary, it was promoted through incentives. The HRA involved 36 questions. Biometric screenings involved measurements of body mass index (BMI kg/m^2), blood pressure (mm Hg), cholesterol (mg/dL), and glucose (mg/dL). The HRA and biometric screenings were provided at no cost to the employees, and were made available on location or with a personal physician. A health nurse or physician assisted the employee in interpreting their HRA and screening results, in order to help guide their need for lifestyle changes and control measures. The current study only considers BMI. Weight classifications are based on commonly accepted ranges of BMI, as follows: underweight (BMI < 18.5), normal weight (BMI 18.5-24), overweight (BMI 25-29), obese (BMI 30-39), and morbidly obese (BMI 40+).

Medical and Pharmacy Claims Data

All active employees received employer-sponsored medical and pharmacy coverage, for themselves and their families. The school district is fully insured with a retained-retention agreement that makes the plan act very much like a self-funded health plan. Each month the district pays a health insurance premium for the cost of healthcare and a small premium for reinsurance of catastrophic claims. Catastrophic claims greater than $250,000 are reinsured by a stop loss policy and are not paid for by the school district. Employee pharmacy data do not

include over-the-counter drugs, but only those medications requiring a prescription. In the United States, a drug is sold over-the-counter if the Food and Drug Administration deems it as sufficiently safe and effective. These medications are not included in the current study. Further, medical and pharmacy cost represents the amount paid by the insurance company as well as copays by the employee.

Statistical Techniques

Counts, means, standard deviations, medians, and percentages were used to describe the study population. Pair-wise comparisons of means were evaluated for statistical significance using the Student-Newman-Keuls Test. Risk ratios compare having a medical and pharmacy cost above the 50^{th} percentile (vs. below), 75^{th} percentile (vs. below), and 90^{th} percentile (vs. below). Statistical significance was determined by the corresponding 95% confidence intervals. For selected medications, the risk of medication use was compared using risk ratios and attributable fraction percentages across the levels of sex, age, and BMI weight classifications. Statistical significance of differences in percent use of selected medications across sex, age, and BMI categories was based on two-sided tests of significance were based on the 0.05 level against a null hypothesis of no association. Data was evaluated using the statistical software package PC-SAS (version 9.4; SAS Institute, Inc., 2014).

Results

In 2010-11, there were 3023 eligible employees, of which 2531 (83.72%) remained employed through the academic year 2013-14. Those more likely to remain employed over the study period were 40-59 years of age and had lower medical and pharmacy costs (Table 1). In 2010-11, ages

ranged from 18-76, with mean age significantly younger for those who remained employed (46.9 vs. 49.2, $p < 0.0001$). Those who remained employed had significantly lower mean medical costs ($3056 vs. $7887, $p < 0.0001$) and mean pharmacy costs ($859 vs. $1105, p =0.0387). The results of this study are based on those continuously employed over the four academic years.

Most employees participated in annual wellness screening (84.1% in 2010-11, 84.4% in 2011-12, 87.6% in 2012-13, and 80.7% in 2013-14). In 2010-11, there was no significant difference in mean medical cost between those who participated in wellness screening and those who did not ($3148 vs. $2571, p = 0.2900). However, median medical cost was significantly greater for those who participated in wellness screening ($588 vs. $470, p = 0.0454). For all academic years, women were 1.03 (95% CI 1.01- 1.06) times more likely than men to complete annual wellness screenings, after adjusting for age and academic year. Participants in wellness screening were significantly younger (M = 47.8 vs. 49.8, $p < 0.0001$), after adjusting for sex and year. Those participating in wellness screening had significantly lower mean medical cost ($3093 vs. $4181, p = 0.0013), but experienced no significant difference in mean annual pharmacy costs, after adjusting for age, sex, and year.

Among participants in annual wellness screening, mean BMI remained constant across the academic years (Table 2). Mean BMI was greater for men than women and in ages 40 years and older. Medical and pharmacy costs were highly positively skewed, with considerable variability. Hence, identifying significant differences in the mean costs across the levels of sex, age, and year, were less likely to occur than to find significant differences in the median costs across the levels of these variables. Medical costs were higher for women than men, increased with age, and were greater in morbidly obese individuals. Pharmacy costs were higher in women than men, increased with age, and were lowest in those of normal weight.

The risk of medical and pharmacy costs above the 50th, 75th, and 90th percentiles are shown according to sex, age, and BMI weight classification in Table 3. Higher BMI has a greater impact on higher percentiles of medical and pharmacy costs. For example, morbidly obese compared with normal weight are 1.13 (13%), 1.30 (30%), and 1.93 (93%) more likely to have pharmacy costs above the 50th, 75th, and 90th percentiles, respectively. Medical and pharmacy costs above these percentiles are greater in women than men and increase with age.

Associations between selected percentiles of medical and pharmacy costs and BMI weight classifications varied according to age (Figure 1), but not sex (data not shown). Greater medical and pharmacy costs with older age groups are seen in the graph. However, the increasing costs with higher age are most pronounced in the underweight and morbidly obese groups.

Medication use is shown across sex, age, and BMI groups in Table 4. For any medication, women were 18% more likely to file a claim than men, employees 60 years of age or older were 23% more likely to file a claim than those less than 40 years, and morbidly obese were 6% more likely to file a claim than those of normal weight. For 22 of the 33 medications considered, the percentage of annual claims was higher for women than men. For high blood pressure and statins was the percentage of claims greater for men than women. For 25 of the medications, the percentage of annual claims increased with age. For 24 of the medications, the percentage of annual claims was associated with BMI (20 positively and 4 negatively). The strongest positive associations involved diabetes, high cholesterol (statins), blood thinners, high blood pressure, and edema. Negative associations involved acne, birth control, Herpes, and osteoporosis. The highest annual percent of acne, antibiotic, cold/influenza/allergy, and eye infection medications occurred in underweight individuals. For edema, muscle spasms, pain, and ulcers, medication use was comparatively high in underweight individuals, dropped for normal weight, and then increased in higher weight classifications.

We also report the attributable fraction in the population. For example, this statistic says that 8.82% of diabetes medication is attributed to being overweight, 20.34% is attributed to being obese, and 30.43% is attributed to being morbidly obese. Where the risk ratio is less than 1, the preventive fraction can be estimated. For example, the risk of requiring osteoporosis medication is lower for obese compared with normal weight employees (i.e., Risk Ratio = 0.54). The corresponding preventive fraction is 66%, meaning in the absence of obesity there would be 66% fewer claims for osteoporosis medication. The attributable fraction in the population and the preventive fraction both assume a cause-and-effect association between exposure and disease.

Discussion

The current study identified the degree to which sex, age, and BMI are associated with medical and pharmacy costs among employees in a large school district. Associations were also evaluated for 33 commonly prescribed medications.[28] The study extends previous research by including certain medications not previously evaluated and considering associations for all BMI weight classifications.

Higher medical and pharmacy costs among women, in older age, and among those not of normal weight is consistent with previous research.[8-10] Greater medical and pharmacy costs with older age are most pronounced in the underweight and morbidly obese groups. Hence, weight management at older ages appears particularly important in terms of lowering medical and pharmacy costs.

Higher medication use in women than men was primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Prescription costs for vitamins/minerals were also noticeably higher in women than men. Family planning and prenatal care may explain the greater use of birth control medications and vitamins/minerals among women. Loss of estrogen in women at older ages and female reproductive hormones may contribute to the higher level of osteoporosis and thyroid disease in women.[29 30]

Medication use was higher in those aged 60 years and older compared with those younger than 40, primarily because of diabetes, edema, high blood pressure, high cholesterol (statins), and thyroid disease. Previous research has shown that the risk of these diseases increase with age.[31-35] Medication use also noticeably increased with age for acid reflux, bowel/rectum, inflammation, and stomach acid. This is consistent with older age tending to be associated with more gastrointestinal problems.[36]

Medication use was highest in those who were morbidly obese. We found positive associations between body weight and higher use of medications for treating acid reflux, fungus, bacterial infections, arthritis, asthma, colds, influenza, allergies, depression, diabetes, edema, high blood pressure, muscle spasms, nausea/vomiting, pain, high cholesterol, stomach acid, thyroid, and ulcers. Other studies have identified a similar associations.[21 24 25 27] Morbidly obese individuals were also more likely to be prescribed vitamins and minerals than normal weight individuals. We did not find an association between body weight and increased use of medication for the bowel/rectum, skin, or urinary tract, which was counter to that found in other studies.[21 37-39] We also assessed but did not find a significant association for medications used to treat anxiety, insomnia, convulsions, or teeth and gums. The insignificant finding for anticonvulsants and teeth and gums may be because of insufficient power (i.e., small numbers).

Finally, we assessed the association between body weight and medications for birth control, herpes, and osteoporosis, wherein significant negative associations were found. We are not aware of other studies that have looked at the association between body weight and medications used for colds, influenza, depression, edema, birth control, herpes, or osteoporosis.

Greater use of medication to treat acid reflux or stomach acid among individuals with higher BMI is consistent with previous research showing hospitalization rates for reflux disease to be positively associated with BMI.[40 41] Another study found that higher BMI was associated with increased gastroesophageal reflux in both normal and overweight individuals.[42] Heavier body weight can add pressure to the stomach and diaphragm, thereby resulting in reflux. Further, increased use of medication for nausea/vomiting among individuals with higher BMI weight classifications is consistent with other research.[43]

The positive association between higher BMI and increased use of medication for ulcers is consistent with other research, particularly peptic (gastric and duodenal) ulcers.[44 45] The mechanism to explain the association between obesity and peptic ulcer disease remains unclear. Obesity is also associated with Helicobacter pylori, which has been linked with gastric ulcers.[46]

Previous research has shown that overweight and obese individuals are at greater risk for infections.[37-49] This is consistent with our findings that show increased use of antibiotics and medication for acne, colds/influenza/allergy, and eye infections among obese individuals. However, it has been shown previously that antibiotics can also weaken the immune system,[50] as well as lead to obesity.[51] Some inflammatory diseases known to be associated with obesity in which we found a positive association between obesity and medication included influenza,[52 53] heart disease,[54] diabetes,[55] allergies,[56-59] asthma,[60] edema,[61-63] and arthritis.[64-67] A compromised immune system may also trigger autoimmune diseases, including rheumatoid arthritis and thyroid disease,[68] as indicated in the current study.

Overweight and obese individuals were more likely to receive cold, influenza, or allergy medication. Obesity is associated with impaired immune response to influenza vaccination in humans.[69] Because vaccination is less successful for obese individuals,[70 71] a greater level of medication may be sought for treating colds, influenza, and allergies.

Overweight and obese individuals received higher levels of pain medication. Research indicates that the nature of the relationship between higher BMI and pain is likely indirect.[72] For example, greater body weight is associated with osteoarthritis, which, in turn, leads to pain.[73] Being overweight or obese may result in greater risk for back pain, joint pain, and muscle spasms.[74] One study also found that obese individuals were more sensitive than those of normal weight to pressure pain.[75]

We found that higher BMI was associated with depression medication, as consistent with previous research.[76-79] In one study, the age-adjusted level of depression among adults (ages 20 and older) in the United States was 43.2% for those with depression compared with 33.0% for those without depression.[80] It may be that higher use of prescription medication for depression among those with greater BMI is partly because these people are more likely to experience other conditions related to depression, such as heart disease and diabetes.[81-83]

There was more use of vitamins/minerals among morbidly obese employees. Of the prescribed vitamins/minerals only 8.0% involved vitamin B and 57.3% involved vitamin D. A previous study showed an association between low vitamin B12 and being obese.[84] Another study found that the prevalence of vitamin D deficiency was 35% greater in obese individuals.[85]

Acne, antibiotic, cold/influenza/allergy, and eye infection medications were prescribed more often for underweight individuals. This is consistent with underweight individuals having poorer nutrition and, consequently, a weakened immune system.[86] For edema, muscle spasms, pain, and ulcers, medication use showed a J-shape relationship with BMI weight classification. Poor nutrition may also explain the higher levels of medication use among underweight individuals for these medications. Despite mean medical costs being similar for those who participated in wellness screening during the first year of the study, over the four academic years, participants in wellness screening ended up having significantly lower mean medical costs. However, pharmacy costs did not go down. It has been shown that wellness screening can cause the number and cost of pharmaceuticals to go up, at least initially, as the need for treatment is identified.[87] Identified treatment needs can then, in turn, help prevent more costly health problems in the future. For example, medications used to treat high blood pressure can result in lowering the risk of diabetes, heart disease, stroke and kidney disease; treatment of insomnia can help lower the risk of irritability, depression or anxiety, difficulty paying attention, and accidents due to increased errors; treatment of high cholesterol with statins can help lower the risk of cardiovascular disease; treatment of oral infections can help reduce the risk of diabetes, cardiovascular disease, and preterm birth; and vitamins/minerals can help prevent a host of diseases (scurvy, rickets, anemia, neural tube defects, pellagra, etc.). High blood pressure and statin medications were among the highest prescribed in our study.

A limitation of this study involves external validity (generalizability). Specifically, the study only considered those individuals who remained employed over all four academic years. These people were generally healthier and in the age range 40-59. The study also focused on those who completed wellness screening because they contained BMI information. These employees were more likely women and younger. In addition, the causal direction between medication use and BMI could not be determined. That is, some medications may have contributed to body mass whereas others were in response to body mass. Finally, the current study did not have information on the use of vitamins or minerals obtained over the counter and small numbers made it impossible to evaluate the relationship between specific types of vitamins/minerals and sex, age, and BMI.

Conclusion

Weight management at older ages, particularly in underweight and morbidly obese individuals, is most important for lowering medical and pharmacy costs. Medical costs decreased, possibly because of effective drug treatment and prevention. Pharmacy costs remained constant, possibly because screening identified a need for certain medications. Greater use of medication among women than men is primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Greater medication use in older age is primarily related to medications used to treat gastrointestinal problems. Medication use was positively associated with BMI for most of the conditions being treated, with exceptions involving birth control, herpes, and osteoporosis. A J-shape relationship between BMI weight classification and medication use for acne, antibiotic, cold/influenza/allergy, eye infection, edema, muscle spasms, pain, and ulcers may be because of poorer nutrition in underweight individuals.

References

1. 2016 Employer Health Benefits Survey. kff.org. http://www.kff.org/health-costs/report/2016-employer-health-benefits-survey/. Published September 14, 2016. Accessed February 21, 2018.
2. Chen L, Hannon PA, Laing SS, Kohn MJ, Clark K, Pritchard S, Harris JR. Perceived workplace health support is associated with employee productivity. Am J Health Promot. 2015;29(3):139-146.
3. Centers for Disease Control and Prevention. cdc.gov. http://www.cdc.gov/sustainability/worksitewellness/ Worksite wellness. Updated December 9, 2014. Accessed March 18, 2018.
4. Michaels CN, Greene AM. Worksite wellness: increasing adoption of workplace health promotion programs. Health Promot Pract. 2013;14(4):473-479.
5. Witt LB, Olsen D, Ablah E. Motivating factors for small and midsized businesses to implement worksite health promotion. Health Promot Pract. 2013;14(6), 876-884.
6. Niessen MA, Kraaijenhagen RA, Dijkgraaf MG, van Pelt D, van Kalken CK, Peek N. Impact of a Web-based worksite health promotion program on absenteeism. J Occup Environ Med. 2012;54(4):404-408.
7. Kaspin LC, Gorman KM, Miller RM. Systematic review of employer-sponsored wellness strategies and their economic and health-related outcomes. Popul Health Manag. 2013;16(1): 14-21.
8. Metge C, Black C, Peterson S, Kozyrskyi AL. The population's use of pharmaceuticals. Med Care. 1999;37(6 Suppl):JS42-JS59.

9. Bertakis K, Azari R, Helms L, Callahan E, Robbins J. Gender differences in the utilization of health care services. J Fam Pract. 2000;49(2):147-152.

10. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Int J Obes. 2005;29(3):334-339.

11. Karmali KN, Lloyd-Jones DM, Berendsen M, et al. Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. JAMA Cardiol. 2016;1(3):341-349.

12. Fretheim A, Odgaard-Jensen, Brørs O, Madsen S, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.

13. Taylor F, Huffman MD, Macedo A, et al. Statins for the primary prevention of cardiovascular disease. Cochrane. 2013. http://www.cochrane.org/CD004816/VASC_statins-primary-prevention-cardiovascular-disease. Accessed February 21, 2018.

14. Czeizel AE. Birth defects are preventable. Int J Med Sci. 2005;2(3):91-92.

15. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029-2043.

16. Asthma. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660. Published March 9, 2018. Accessed February 24, 2018.

17. Arthritis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/arthritis/diagnosis-treatment/drc-20350777. Published March 7, 2018. Accessed February 24, 2018.

18. Preventive Medicine Reports Paper

19. Thompson D, Edelsberg J, Colditz GA, Bird AP, Oster G. Lifetime health and economic consequences of obesity. Arch Intern Med. 1999;11;159(18):2177-2183.

20. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009;121(6):21-33.

21. Kinge JM, Morris S. Association between obesity and prescribed medication use in England. Econ Hum Biol. 2014;15:47-55.

22. Narbro K, Agren G, Jonsson E, et al. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. Arch Intern Med. 2002;162(18):2061-2069.

23. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff. 2009;28(5):w822-31.

24. Randhawa AK, Parikh JS, Kuk JL. Trends in medication use by body mass index and age between 1988 and 2012 in the United States. PLoS One. 2017 Sep 20;12(9):e0184089.

25. Kit BK, Ogden CL, Flegal KM. Prescription medication use among normal weight, overweight, and obese adults, United States, 2005-2008. Ann Epidemiol. 2012;22(2):112-119.

26. Jarrett B, Bloch GJ, Bennett D, Bleazard B, Hedges D. The influence of body mass index, age and gender on current illness: a cross-sectional study. Int J Obes. 2010;34(3):429-436.

27. Raebel MA, Malone DC, Conner DA, Xu S, Porter JA, Lanty FA. Health services use and health care costs of obese and nonobese individuals. Arch Intern Med. 2004;164(19):2135-2140.

28. Fuentes AV, Pineda MD, Venkata KCN. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. Pharmacy (Basel). 2018;6(2):E43.

29. Alswat KA. Gender disparities in osteoporosis. Clin Med Res. 2017;9(5): 382–387.

30. Li H, Li J. Thyroid disorders in women. Minerva Med. 2015;106(2):109-114.

31. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650-2664.

32. Trayes KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. Am Fam Physician. 2013;88(2):102-110.

33. Mc Donald Posso AJ, Motta Borrel JA, Fontes F, Cruz Gonzalez CE, Pachón Burgos AA, Cumbrera Ortega A. High blood pressure in Panama: Prevalence, sociodemographic and biologic profile, treatment, and control (STROBE). Medicine (Baltimore). 2014;93(22): e101.

34. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984-1994. Circulation. 1997;96(1):37-43.

35. Gesing A. The thyroid gland and the process of aging. Thyroid Res. 2015;8(Suppl 1):A8.

36. A L D'Souza. Ageing and the gut. Postgrad Med J. 2007; 83(975):44–53.

37. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916.

38. Brown J, Wimpenny P, Maughan H. Skin problems in people with obesity. Nurs Stand. 2004;18(35):38-42.

39. Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. Urology. 2012;79(2):266-269.

40. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup

Study. First National Health and Nutrition Examination Survey. Ann Epidemiol. 1999;9(7):424-435.

41. Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Alim Pharmacol Ther. 2013;37(5):555-563.

42. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Association between body mass index and gastroesophageal reflux symptoms in both normal weight and overweight women. N Engl J Med. 2006;354(22):2340-2348.

43. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol 2004;99(9):1807-1814.

44. Boylan MR, Khalili H, Huang ES, Chan AT. Measures of adiposity are associated with increased risk of peptic ulcer. Clin Gastroenterol Hepatol. 2014 Oct;12(10):1688-1694.

45. Kim J, Kim KH, Lee BJ. Association of peptic ulcer disease with obesity, nutritional components, and blood parameters in the Korean population. PLoS One. 2017;12(8): e0183777.

46. Xu M, Liu L, Yuan B, Yin J, Lu Q. Association of obesity with Helicobacter pylori infection: A retrospective study. World J Gastroenterol 2017;23(15):2750-2756.

47. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006;6(7)438-446.

48. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes. 2013;37:333-340.

49. Lübbeke A, Zingg M, Hoffmeyer P, et al. Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthopaedica. 2016;87(2):132-138

50. Yang JH, Bhargava P, McCloskey D, Mao N, Palsson BO, Collins JJ. Antibiotic-induced changes to the host metabolic environment inhibit drug efficacy and alter immune function. Cell Host & Mocrobe. 2017;22(6):757-765.

51. Early G. Current Evidence regarding antibiotic exposure and childhood obesity: an integrative review. Ped Nurs. 2017;43(4):169-174.

52. Bandaru P, Rajkimar H, Napanveettil G. The impact of obesity on immune response to infection and vaccine: an insight into plausible mechanisms. Endocrinol Metab Synd 2013;2:2.

53. Kwong JC, Campitelli MA, Rosella LC. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada: a cohort study. Clin Infect Dis. 2011;53(5):413-421.

54. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010;2010:535918.

55. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.

56. Ciprandi G, Pistorio A, Tosca M, Ferraro MR, Cirillo I. Body mass index, respiratory function and bronchial hyperactivity in allergic rhinitis and asthma. Respir Med 2009;103(2):289-295.

57. Gorgievska-Sukarovska B, Lipozencić J, Susac A. Obesity and allergic diseases. Acta Dermatovenerol Croat. 2008;16(4):231-235.

58. Shah R, Yang Y. Health and economic burden of obesity in elderly individuals with asthma in the United States. Popul Health Manag 2015;18(3):186-191.

59. Guo Y, Moon JY, Laurie CC, et al. Genetic Predisposition to Obesity is associated with Asthma in US Hispanics/Latinos: Results from the Hispanic Community Health Study/Study of Latinos. Allergy. 2018;doi: 10.1111/all.13450. [Epub ahead of print]

60. Rodriguez D. Obesity and Asthma – What's the Connection. https://www.everydayhealth.com/asthma/obesity-connection.aspx. Published August 28, 2013. Accessed April 12, 2018.

61. Greene, A.K., et al. Lower-Extremity Lymphedema and Elevated Body-Mass Index. N Engl J Med. 2012;366:2136-2137.

62. Helyer, L.K., et al. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. Breast J. 2012;16(1):48-54.

63. Greene AK, Grant FD, Slavin SA, Maclellan RA. Obesity-induced lymphedema: clinical and lymphoscintigraphic features. Plast Reconstr Surg. 2015;135(6):1715-1719.

64. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138(2):185-193.

65. Baodong Qin, Min Yang, Haitao Fu, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17(1):86.

66. Feng J, Chen Q, Yu F, et al. Body mass index and risk of rheumatoid arthritis: a meta-analysis of observational studies. Medicine. 2016;95(8):e2859.

67. Albrecht K, Richter A, Callhoff J, et al. Body mass index distribution in rheumatoid arthritis: a collaborative analysis from three large German rheumatoid arthritis databases. Arthritis Res Ther. 2016;18:149.

68. Rodriguez D. How Your Immune System Worsens Arthritis. EverydayHealth.com. https://www.everydayhealth.com/arthritis/understanding/the-immune-system.aspx. Published August 1, 2012. Accessed April 11, 2018.

69. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes. 2012;36(8):1072-1077.

70. Painter SD, Ovsyannikoa IG, Poland GA. The weight of obesity on the human immune response to vaccination. Vaccine. 2015;33(36): 4422–4429.

71. Young KM, Gray CM, Bekker LG. Is Obesity a Risk Factor for Vaccine Non-Responsiveness? PLoS One. 2013;8(12): e82779.

72. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8:399-408.

73. Erdmann J. Osteoarthritis and Obesity. www.arthritis.org. https://www.arthritis.org/living-with-arthritis/comorbidities/obesity-arthritis/osteoarthritis-and-obesity.php. Accessed April 11, 2018.

74. American Obesity Association. Health effects of obesity. AOA Fact Sheets. 2002.

75. Tashani OA, Asitita R, Sharp D, Johnson MI. Body mass index and distribution of body fat can influence sensory detection and pain sensitivity. Eur J Pain 2017;21(7):1186-1196.

76. Rathee N. Obesity and depression: Are they related? Indian J Health Well. 2017;8(12):1472-1475.

77. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. Int J Obesity. 2009;33(2):257-266.

78. Onyike CU, Crum RM, Lee HB, Lyketsos DG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003;158(12):1139-1147.

79. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2008;70(3):288-297.

80. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005-2010. NCHS Data Brief, No. 167, October 2014.

81. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry 2004;65(5):634-651.

82. Ferraro KF, Su Y, Gretebeck RJ, Black DR, Badylak SF. Body mass index and disability in adulthood: A 20-year panel study. Am J Public Health. 2002;92(5):834-840.

83. Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. J Psychosom Res. 2002;53(4):859-863.

84. Baltaci D, Kutlucan A, Turker Y, et al. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Med Glas. 2013;10(2):203-210.

85. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341-349.

86. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? The Lancet 2003;361:2226-2234.

87. Merrill RM, Telford CT. Pharmaceutical use according to participation in worksite wellness screening and health campaigns. Prev Med Rep 2018;12:158-163.

Footnotes

Contributors: RMM conceived and designed the epidemiological study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. RPF interpreted the data, provided a literature review, and revised the manuscript. Both authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by both authors.

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Table 1 Characterization of the study group according to sex, age, medical and pharmacy costs

	No.	%	Continuously Employed %	Chi-square p value	Risk Ratio	95% CI
Sex						
Men	797	26.36	84.69	0.3884	1.00	
Women	2226	73.64	83.38		0.98	0.95-1.02
Age Group						
18-39	770	25.47	82.21	< 0.0001	1.00	
40-49	806	26.66	89.45		1.09	1.05-1.13
50-59	1088	35.99	88.24		1.07	1.03-1.12
60-76	359	11.88	60.45		0.74	0.67-0.80
Medical Cost (USD)						
0-184	755	25.0	87.55	< 0.0001	1.00	
185-604	757	25.0	85.07		0.97	0.93-1.01
605-2049	755	25.0	84.64		0.97	0.93-1.01
2050-7191	454	15.0	79.30		0.91	0.86-0.96
7192+	302	10.0	75.17		0.86	0.80-0.92
Pharmacy Cost (USD)						
0-6	759	25.0	86.92	< 0.0001	1.00	
7-194	755	25.0	85.21		0.99	0.69-1.03
195-903	755	25.0	82.59		0.96	0.92-1.00
904-2303	452	15.0	84.14		0.99	0.94-1.04
2304+	302	10.0	74.92		0.86	0.80-0.93

Sex, age, medical and pharmacy costs apply to the 2010-11 academic year.

Table 2 Medical and pharmacy costs according to sex, age, year, and body mass index

	BMI (kg/m²)			Medical Cost (USD)				Median one-way analysis	Pharmacy Cost (USD)				Median one-way analysis
	Mean	SD	SNK	Mean	SD	SNK	Median	p value	Mean	SD	SNK	Median	p value
Sex													
Men	29.35	5.80	A	2869	10581	A	373	< 0.0001	725	2324	A	53	< 0.0001
Women	27.26	6.47	B	3447	12049	A	741		963	3550	B	238	
Age Group													
18-39	27.17	6.06	A	2236	9344	A	389	< 0.0001	660	3342	A	70	< 0.0001
40-49	27.76	6.42	B	3052	12366	B	503		750	2806	A	106	
50-59	28.05	6.55	B	3935	12579	B	845		1021	3288	B	261	
60-76	28.17	6.13	B	3749	10831	B	989		1288	3990	C	344	
Year													
2010-11	27.89	6.40	A	3188	10524	A	605	0.2313	830	2247	A	195	0.0016
2011-12	27.79	6.31	A	3621	12816	A	610		953	3180	A	189	
2012-13	27.87	6.59	A	3208	11836	A	670		934	3571	A	173	
2013-14	27.63	6.16	A	3191	11557	A	651		894	3913	A	141	
BMI (kg/m²)													
Underweight				2191	1190	A	647	0.0003	1454	6706	A	224	0.0004
Normal weight				2826	333	A	650		779	3285	B	167	
Overweight				3174	514	A	603		926	3085	A, B	169	
Obese				3544	459	A	665		1031	3458	A, B	228	
Morbidly obese				6911	2092	B	1033		853	1493	A, B	242	

SNK: Student-Newman-Keuls Test. Different letters in the SNK columns indicate significant difference among the levels of the variables at the 0.05 level.

Table 3 Risk of medical and pharmacy costs (USD) above the 50th, 75th, and 90th percentiles according to BMI weight classification, sex, and age

	Medical						Pharmacy					
	50th percentile Above vs. below		75th percentile Above vs. below		90th percentile Above vs. below		50th percentile Above vs. below		75th percentile Above vs. below		90th percentile Above vs. below	
	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI
Sex												
Men	1.00		1.00		1.00		1.00		1.00		1.00	
Women	1.43	1.36-1.51	1.47	1.35-1.60	1.42	1.24-1.64	1.58	1.50-1.66	1.59	1.46-1.74	1.14	1.00-1.29
Age Groups												
18-39	1.00		1.00		1.00		1.00		1.00		1.00	
40-49	1.16	1.08-1.23	1.15	1.03-1.29	1.08	0.90-1.28	1.14	1.07-1.22	1.45	1.29-1.64	1.72	1.37-2.15
50-59	1.50	1.42-1.59	1.65	1.50-1.82	1.36	1.16-1.58	1.48	1.39-1.56	2.28	2.05-2.55	2.82	2.30-3.46
60+	1.61	1.52-1.72	1.83	1.64-2.04	1.33	1.11-1.60	1.57	1.48-1.68	2.57	2.29-2.89	3.78	3.06-4.68
BMI (kg/m^2)												
Underweight	1.05	0.88-1.26	0.91	0.64-1.31	0.61	0.28-1.35	2.05	1.25-3.34	1.05	0.74-1.48	2.05	1.25-3.34
Normal weight	1.00		1.00		1.00		1.00		1.00		1.00	
Overweight	0.95	0.90-1.00	0.95	0.86-1.05	1.01	0.85-1.20	1.01	0.95-1.06	1.18	1.07-1.30	1.68	1.41-2.00
Obese	1.00	0.95-1.06	1.14	1.03-1.25	1.21	1.01-1.43	1.11	1.05-1.17	1.19	1.08-1.31	1.76	1.47-2.12
Morbidly obese	1.18	1.08-1.29	1.62	1.40-1.87	2.18	1.72-2.77	1.13	1.03-1.25	1.30	1.09-1.55	1.93	1.43-2.61

Shaded cells represent statistical significance at the 0.05 level.

Table 4 Medication use according to sex, age, and BMI weight classification

		Sex		Age Group				Body Mass Index (kg/m²)				
		Men	Women	18-39	40-49	50-59	60+	Underweight	Normal weight	Over weight	Obese	Morbidly obese
Medication	%											
Acid Reflux	5.75	5.56	5.81	3.02	4.54	7.14	8.36	3.57	4.34	5.36	7.19	9.14
Risk ratio		1.00	1.04	1.00	1.50	2.36	2.77	0.82	1.00	1.24	1.66	2.11
AF_p (%)		0.00	0.26	0.00	2.81	7.27	9.23		0.00	1.33	3.64	5.98
Acne	7.17	3.15	8.62	7.15	7.03	7.16	7.40	9.82	8.81	6.64	6.34	6.18
Risk ratio		1.00	2.74	1.00	0.98	1.00	1.03	1.11	1.00	0.75	0.72	0.70
AF_p (%)		0.00	11.07	0.00		0.01	0.25	0.82	0.00			
Antibiotic	21.21	17.81	22.44	18.72	20.76	22.76	21.93	25.89	20.54	20.74	23.73	21.24
Risk ratio		1.00	1.26	1.00	1.11	1.22	1.17	1.26	1.00	1.01	1.16	1.03
AF_p (%)		0.00	5.23	0.00	2.26	4.38	3.51	5.24	0.00	0.21	3.19	0.72
Anticonvulsants	1.49	1.39	1.53	1.84	1.32	1.45	1.40	2.68	1.25	1.13	1.65	1.61
Risk ratio		1.00	1.10	1.00	0.72	0.79	0.76	2.14	1.00	0.90	1.32	1.29
AF_p (%)		0.00	0.15	0.00				1.68	0.00		0.47	0.43
Antifungal	5.29	2.61	5.81	5.64	6.03	4.24	3.87	5.36	5.83	3.81	6.24	6.18
Risk ratio		1.00	2.23	1.00	1.07	0.75	0.69	0.92	1.00	0.65	1.07	1.06
AF_p (%)		0.00	6.09	0.00	0.36				0.00		0.37	0.32
Anxiety	7.88	6.31	8.45	6.42	7.80	8.36	8.97	8.93	7.22	7.11	7.29	6.45
Risk ratio		1.00	1.34	1.00	1.21	1.30	1.40	1.24	1.00	0.98	1.01	0.89
AF_p (%)		0.00	2.60	0.00	1.67	2.33	3.03	1.83	0.00		0.08	
Arthritis	11.06	11.13	11.03	7.72	10.53	12.83	12.56	7.14	9.36	10.72	13.84	14.78
Risk ratio		1.00	0.99	1.00	1.36	1.66	1.63	0.76	1.00	1.15	1.48	1.58
AF_p (%)		0.00		0.00	3.87	6.82	6.48		0.00	1.58	5.03	6.02
Asthma	8.61	7.19	9.13	7.48	8.80	8.00	11.22	6.25	6.24	8.74	10.39	10.75

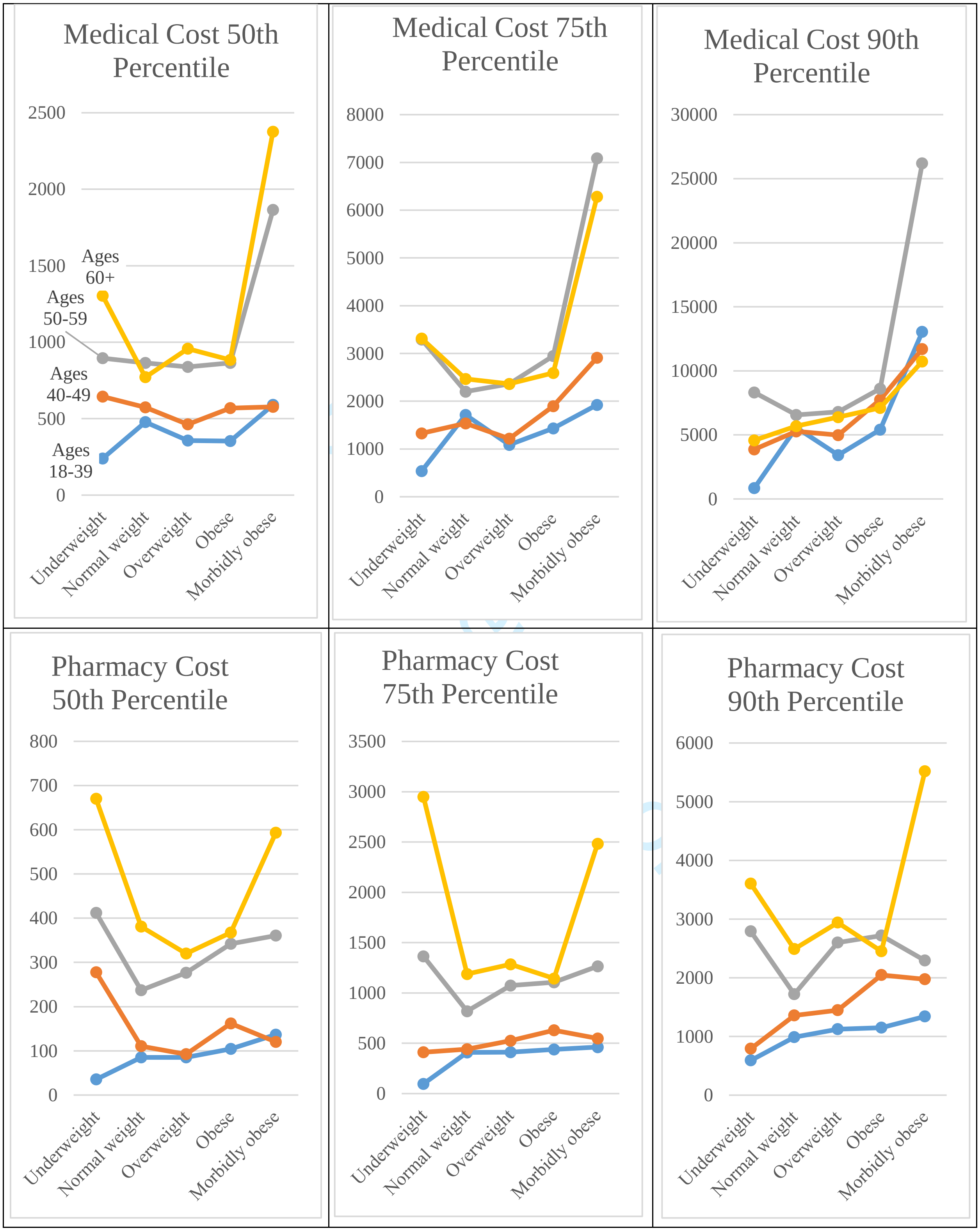
Risk ratio		1.00	1.27	1.00	1.18	1.07	1.50	1.00	1.00	1.40	1.67	1.72
AF_p (%)		0.00	2.27	0.00	1.50	0.59	4.13	0.01	0.00	3.33	5.42	5.86
Birth Control	8.71	0.24	10.88	21.13	8.77	2.59	0.95	10.71	11.69	7.30	6.34	6.99
Risk ratio		1.00	45.33	1.00	0.42	0.12	0.04	0.92	1.00	0.62	0.54	0.60
AF_p (%)		0.00	79.43	0.00					0.00			
Blood Thinner	1.26	1.85	1.05	3.91	18.75	45.31	32.03	0.95	0.52	1.15	2.08	5.22
Risk ratio		1.00	0.57	1.00	4.80	11.59	8.19	1.83	1.00	2.21	4.00	10.04
AF_p (%)		0.00		0	4.56	11.77	8.31	1.03	0	1.50	3.64	10.22
Bowel/Rectum	3.06	2.75	3.17	1.76	2.84	3.53	4.15	1.79	3.15	2.87	2.85	2.96
Risk ratio		1.00	1.15	1.00	1.61	2.01	2.36	0.57	1.00	0.91	0.90	0.94
AF_p (%)		0.00	0.47	0.00	1.84	2.99	3.99		0.00			
Cold/Influenza/Allergy	17.80	14.52	18.99	15.73	18.30	18.14	19.07	22.32	15.53	18.56	20.38	22.04
Risk ratio		1.00	1.31	1.00	1.16	1.15	1.21	1.44	1.00	1.20	1.31	1.42
AF_p (%)		0.00	5.20	0.00	2.83	2.65	3.64	7.22	0.00	3.36	5.27	6.94
Depression	18.24	10.28	21.14	12.51	19.30	20.75	18.84	15.18	16.20	17.59	20.83	18.55
Risk ratio		1.00	2.06	1.00	1.54	1.66	1.51	0.94	1.00	1.09	1.29	1.15
AF_p (%)		0.00	16.16	0.00	9.01	10.73	8.45		0.00	1.54	4.95	2.58
Diabetes	6.32	6.48	6.22	2.53	4.50	7.82	10.94	1.79	2.24	5.67	11.29	17.74
Risk ratio		1.00	0.96	1.00	1.78	3.09	4.32	0.80	1.00	2.53	5.04	7.92
AF_p (%)		0.00		0.00	4.69	11.67	17.36		0.00	8.82	20.34	30.43
Edema	5.14	3.12	5.87	2.04	3.64	6.48	8.86	6.25	3.08	4.66	7.29	12.90
Risk ratio		1.00	1.88	1.00	1.78	3.18	4.34	2.03	1.00	1.51	2.37	4.19
AF_p (%)		0.00	4.33	0.00	3.88	10.06	14.66	5.02	0.00	2.57	6.56	14.08
Eye Infection	12.01	9.23	12.87	11.44	13.06	11.13	12.34	14.29	11.02	12.12	13.64	9.68
Risk ratio		1.00	1.39	1.00	1.14	0.97	1.08	1.30	1.00	1.10	1.24	0.88
AF_p (%)		0.00	4.52	0.00	1.67		0.94	3.44	0.00	1.18	2.78	
Herpes	6.30	3.26	6.86	4.82	7.24	6.12	4.71	1.79	7.66	7.22	4.20	1.88
Risk ratio		1.00	2.10	1.00	1.50	1.27	0.98	0.23	1.00	0.94	0.55	0.25
AF_p (%)		0.00	6.50	0.00	3.07	1.67			0.00			
High Blood Pressure	16.49	19.95	15.60	4.58	11.05	22.78	29.39	6.25	8.54	17.44	24.68	31.99
Risk ratio		1.00	0.78	1.00	2.41	4.97	6.42	0.73	1.00	2.04	2.89	3.75
AF_p (%)		0.00		0.00	18.89	39.59	47.18		0.00	14.66	23.76	31.17

Inflammation	1.19	0.68	1.37	0.69	0.87	1.50	1.68	1.79	0.98	1.40	0.80	1.61
Risk ratio		1.00	2.01	1.00	1.26	2.17	2.43	1.83	1.00	1.43	0.82	1.64
AF_p (%)		0.00	1.19	0.00	0.31	1.38	1.68	0.97	0.00	0.51		0.76
Insomnia	4.23	2.24	4.95	2.70	3.60	5.72	4.04	8.93	4.07	3.92	3.85	4.84
Risk ratio		1.00	2.21	1.00	1.33	2.12	1.50	2.19	1.00	0.96	0.95	1.19
AF_p (%)		0.00	4.87	0.00	1.39	4.52	2.06	4.81	0.00			0.79
Muscle Spasms	4.34	3.53	4.64	3.11	4.57	4.93	4.37	5.36	3.29	4.27	5.44	6.99
Risk ratio		1.00	1.31	1.00	1.47	1.59	1.41	1.63	1.00	1.30	1.65	2.12
AF_p (%)		0.00	1.35	0.00	2.00	2.48	1.73	2.66	0.00	1.28	2.76	4.65
Nausea/Vomiting	5.01	3.77	5.47	5.44	4.85	4.83	5.10	4.46	4.14	4.50	6.19	5.65
Risk ratio		1.00	1.45	1.00	0.89	0.89	0.94	1.08	1.00	1.09	1.50	1.36
AF_p (%)		0.00	2.21	0.00				0.39	0.00	0.43	2.42	1.79
Opioids	17.04	15.98	17.42	14.14	16.29	18.62	18.73	17.86	13.39	15.77	20.28	27.69
Risk ratio		1.00	1.09	1.00	1.15	1.32	1.32	1.33	1.00	1.18	1.51	2.07
AF_p (%)		0.00	1.51	0.00	2.53	5.12	5.24	5.38	0.00	2.94	8.06	15.40
Osteoporosis	1.21	0.07	1.63	0.00	0.17	1.30	4.37	0.89	1.56	1.20	0.85	0.00
Risk ratio		1.00	23.29	1.00				0.57	1.00	0.77	0.54	0.00
AF_p (%)		0.00	21.24	0.00					0.00			
Pain – non opioid	2.19	1.63	2.39	2.78	2.15	1.98	1.91	3.57	1.73	1.67	2.55	2.96
Risk ratio		1.00	1.47	1.00	0.77	0.71	0.69	2.06	1.00	0.97	1.47	1.71
AF_p (%)		0.00	1.01	0.00				2.28	0.00		1.03	1.53
Skin	6.84	4.88	7.55	5.44	6.44	7.37	8.24	6.25	7.25	6.41	7.19	5.38
Risk ratio		1.00	1.55	1.00	1.18	1.35	1.51	0.86	1.00	0.88	0.99	0.74
AF_p (%)		0.00	3.61	0.00	1.24	2.37	3.40		0.00			
Statins	14.49	17.93	13.24	2.31	8.53	20.58	28.4	3.81	7.02	17.95	19.89	27.47
Risk ratio		1.00	0.74	1.00	3.69	8.91	12.29	0.54	1.00	2.56	2.83	3.91
AF_p (%)		0.00		0.00	28.07	53.40	62.07		0.00	18.41	20.99	29.68
Stomach Acid	1.19	1.49	1.07	0.86	1.25	0.99	1.96	0.89	0.81	1.01	1.90	1.08
Risk ratio		1.00	0.72	1.00	1.45	1.15	2.28	1.10	1.00	1.25	2.35	1.33
AF_p (%)		0.00		0.00	0.54	0.18	1.50	0.12	0.00	0.29	1.58	0.40
Teeth/Gums	0.43	0.37	0.46	0.37	0.35	0.43	0.67	0.00	0.27	0.43	0.35	0.27
Risk ratio		1.00	1.24	1.00	0.95	1.16	1.81	0.00	1.00	1.59	1.30	1.00

AF_p (%)		0.00	0.10	0.00		0.07	0.35		0.00	0.25	0.13	0.00
Thyroid	12.76	2.99	16.31	4.37	11.19	16.92	17.61	6.25	13.97	12.74	13.94	19.09
Risk ratio		1.00	5.45	1.00	2.56	3.87	4.03	0.45	1.00	0.91	1.00	1.37
AF_p (%)		0.00	36.24	0.00	16.61	26.82	27.88		0.00			4.47
Ulcers	9.38	8.55	9.69	8.30	8.28	10.19	10.88	10.71	7.59	9.90	10.99	15.32
Risk ratio		1.00	1.13	1.00	1.00	1.23	1.31	1.41	1.00	1.30	1.45	2.02
AF_p (%)		0.00	1.24	0.00		2.09	2.83	3.71	0.00	2.78	4.03	8.72
Urinary Tract Infection	3.01	0.20	4.44	3.39	3.08	3.45	3.25	6.25	3.83	2.83	3.50	3.76
Risk ratio		1.00	22.20	1.00	0.91	1.02	0.96	1.63	1.00	0.74	0.91	0.98
AF_p (%)		0.00	38.95	0.00		0.05		1.87	0.00			
Vitamins/Minerals	2.07	0.71	2.57	2.49	1.73	1.88	2.47	0.00	2.07	1.28	1.75	5.38
Risk ratio		1.00	3.62	1.00	0.69	0.76	0.99	0.00	1.00	0.62	0.85	2.60
AF_p (%)		0.00	5.14	0.00					0.00			3.20
All prescriptions	80.87	71.40	84.32	71.52	78.45	85.24	88.00	83.93	81.46	81.28	83.47	86.29
Risk ratio		1.00	1.18	1.00	1.10	1.19	1.23	1.03	1.00	1.00	1.02	1.06
AF_p (%)		0.00	12.77	0.00	7.27	13.43	15.71	2.39	0.00		1.96	4.58

AF_p: Attributable fraction in the population. Shaded cells represent statistical significance at the 0.05 level. Cells that are left blank had a negative AF_p. In these cases the preventive fraction ([Risk Ratio – 1] × 100) is more appropriate.

Figure 1. Median medical and pharmacy cost (USD) according to Body Mass Index weight classifications and age


Medical Cost 50th Percentile
2500
2000
1500
1000
500
0
Ages 60+
Ages 50-59
Ages 40-49
Ages 18-39
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Medical Cost 75th Percentile
8000
7000
6000
5000
4000
3000
2000
1000
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Medical Cost 90th Percentile
30000
25000
20000
15000
10000
5000
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Pharmacy Cost 50th Percentile
800
700
600
500
400
300
200
100
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Pharmacy Cost 75th Percentile
3500
3000
2500
2000
1500
1000
500
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Pharmacy Cost 90th Percentile
6000
5000
4000
3000
2000
1000
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page/line numbers
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1/6, 2/25
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Done
Objectives	3	State specific objectives, including any prespecified hypotheses	Done
Methods			
Study design	4	Present key elements of study design early in the paper	Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Done
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done
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	Done
Bias	9	Describe any efforts to address potential sources of bias	Done
Study size	10	Explain how the study size was arrived at	Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Done
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
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	Done
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Done
		(c) Summarise follow-up time (eg, average and total amount)	Done
Outcome data	15*	Report numbers of outcome events or summary measures over time	Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Done

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Done
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
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	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done
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	Done

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

BMJ Open

To what extent does sex, age, and BMI impact medical and pharmacy costs? A retrospective cohort study involving employees in a large school district in the United States

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To what extent does sex, age, and BMI impact medical and pharmacy costs? A retrospective cohort study involving employees in a large school district in the United States

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Keywords: body mass index, obesity, prevention, pharmaceuticals, screening

Word count: 3527

Objective To identify the extent that sex, age, and body mass index (BMI) is associated with medical and pharmacy costs.

Design Retrospective cohort.

Setting A school district in the Western United States involving 2531 workers continuously employed during 2011-2014.

Main outcome measures Medical and pharmacy costs and BMI.

Results Approximately 84% of employees participated in wellness screening. Participants were 1.03 (95% CI 1.01- 1.06) times more likely to be women and younger (M = 47.8 vs. 49.8, $p < 0.001$). Median medical and pharmacy costs were higher for women than men, increased with age, and were greater in morbidly obese individuals ($p < 0.001$). Annual pharmacy claims were 18% more likely to be filed by women than men, 23% more likely filed by those aged ≥60 versus <40 years, and 6% more likely filed by morbidly obese individuals than of normal weight ($p < 0.001$) individuals. Greater medical and pharmacy costs in older age were most pronounced in underweight and morbidly obese groups. Higher use of medication among women than men was primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Higher medication use in older age was primarily related to medications used to treat gastrointestinal problems. Medication use was positively associated with BMI weight classifications for most of the 33 drug types considered, with exceptions involving birth control, herpes, and osteoporosis. A J-shape relationship was observed between BMI and medication use for acne, antibiotic, cold/influenza/allergy, eye infection, edema, muscle spasms, pain, and ulcers.

Conclusions Medications associated with higher medical and pharmacy costs among women, older age, and underweight or obese individuals are identified. Lowering medical and pharmacy

costs requires weight management in older ages, particularly for underweight and obese. Higher pharmacy costs for certain drugs among underweight individuals may be associated with poorer nutrition.

Strengths and limitations of this study

- A large cohort of employees was available for retrospective assessment of the association between sex, age, and BMI with medical and pharmacy costs.
- The association between sex, age, and 33 specific types of medication were assessed, some of which have not been previously considered.
- All active employees received employer-sponsored medical and pharmacy coverage, and above 84% had information that allowed us to determine body mass.
- A few medications may have contributed to weight gain, which we were unable to adjust for in the current study.
- The study population and patterns of prescription drug use may limit generalization of the results.

Introduction

Many companies offer wellness-screening programs consisting of health risk assessment and biometric screening. The 2016 Employer Health Benefits Survey found that among large firms (200 or more employees) in the United States, 59% offered health risk assessment (of which 32% had an incentive component) and 53% offered biometric screening (of which 31% included an incentive component).[1] These programs are intended to promote a greater sense of personal responsibility for lifestyle choices, identify the need for health behavior change, reduce future health problems, encourage patient management of existing health problems, decrease worker absenteeism, and improve job satisfaction and worker productivity.[2-7] Larger companies are also required to offer employer-sponsored medical and pharmacy coverage for their employees. Hence, information obtained on the health risk assessment and screenings can be compared with the medical and pharmacy costs.

Medical and pharmacy costs are influenced by a number of factors, including sex, age, and Body Mass Index (BMI).[8-10] Although medical costs are often a response to acute and chronic health conditions, pharmaceutical costs are often used to prevent more serious health problems. For example, antihypertensive medication, or statins, are useful in preventing cardiovascular disease;[11-13] multivitamins or folic acid for preventing congenital abnormalities;[14] aspirin and non-steroidal anti-inflammatory for preventing colorectal cancer;[15] bronchodilators, steroids, and anti-inflammatories for managing asthma;[16] and nonsteroidal anti-inflammatory drugs, steroids, analgesics, and immunosuppressive drugs for managing arthritis.[17] Consequently, wellness screening may actually increase use of prescription medication.[18]

Although a person's body weight may be associated with increased risk for various chronic health conditions and poorer health-related quality of life,[19 20] only in the last 15 years or so has its impact on healthcare expenditures been assessed.[10] Further, only a small number of studies have explored the association between body weight and prescription drug use. A study conducted in England found that overweight and obese individuals were more likely to receive medication for the cardiovascular system; gastrointestinal system; respiratory system; central nervous system; endocrine system; gynecology/urinary disorders; musculoskeletal and joint disorders; infections; eye, ear and oropharynx problems; and skin disorders.[21] A study in Sweden showed that use and cost of medication in general are significantly greater in obese individuals.[22] A study in the United States found that obesity was responsible for $7 billion in Medicare prescription drug costs in 2006.[23] Another study conducted in the United States identified increased medication use during 1988 through 2012, with the increase most prominent among obese individuals.[24] A large cross-sectional study of 9789 adults in the National Health and Nutrition Examination Survey (NHANES) found that obese individuals utilize several prescription drugs (e.g., hypertension, lipid-lowering, and diabetes medications) more frequently than normal weight individuals.[25] Another study based on NHANES data found that while medication use increased over time for obese individuals compared with normal weight individuals ages 40 years and older, the increase was only marginal for those aged 25-39 years.[26] One study found that obese individuals used more analgesic, asthma, cardiovascular, diabetes, intranasal allergic rhinitis, thyroid, and ulcer medications.[27]

The purpose of the current study was to identify the extent to which sex, age, and BMI weight classifications are associated with medical and pharmacy costs among a large group of teachers, administrators, and other school staff. These associations are also evaluated for 33 more

commonly prescribed medications.[28] Although studies have previously looked at the association between BMI and prescription medications, we evaluated some drugs that have not been formerly considered, and the breadth of drugs covered is greater than in past studies. In addition, evaluating the effect of being underweight on medical and pharmacy costs, and on specific drug types, is unique to this study.

Methods

Patient and Public Involvement

A retrospective cohort study was conducted that associated sex, age, and BMI with medical and pharmacy cost data for employees of a large school district in the western United States. Specific patients and or the general public was not involved in this study. Body mass index was obtained from those employees who participated in wellness screening. Employer-sponsored insurance was available to all employees. The school district comprised six high schools, eight junior high schools, and 31 elementary schools. Employees consisted of approximately three teachers to every one staff member (cooks, bus drivers, grounds keepers, maintenance workers, administrators, clerical workers, etc.). We were not provided specific job type and salary for each employee. However, we can assume that the teachers, administrators, counselors, and nurses, who represent almost all of the employees, had at least a college degree, that their salaries are commensurate with other school districts, and that the employer-sponsored insurance coverage was not strongly impacted by the employee's income or education.

The study involved the academic years 2010-11, 2011-12, 2012-13, and 2013-14. Employees were offered wellness screenings (personal health risk assessment [HRA] and biometric evaluation) each fall. Medical and pharmacy claims data were also obtained for the

employees in each academic year. Wellness screening and claims data were combined with a file of eligible employees and assessed within each academic year. The eligibility file contained information on current employment, sex, age, and year.

Wellness Screening

All employees were offered wellness screening. Although participation was voluntary, it was promoted through incentives. The HRA involved 36 questions. Biometric screenings involved measurements of body mass index (BMI kg/m^2), blood pressure (mm Hg), cholesterol (mg/dL), and glucose (mg/dL). The HRA and biometric screenings were provided at no cost to the employees, and were made available on location or with a personal physician. A health nurse or physician assisted the employee in interpreting their HRA and screening results, in order to help guide their need for lifestyle changes and control measures. The current study only considers BMI. Weight classifications are based on commonly accepted ranges of BMI, as follows: underweight (BMI < 18.5), normal weight (BMI 18.5-24), overweight (BMI 25-29), obese (BMI 30-39), and morbidly obese (BMI 40+).

Medical and Pharmacy Claims Data

All active employees received employer-sponsored medical and pharmacy coverage, for themselves and their families. The school district is fully insured with a retained-retention agreement that makes the plan act very much like a self-funded health plan. Each month the district pays a health insurance premium for the cost of healthcare and a small premium for reinsurance of catastrophic claims. Catastrophic claims greater than $250,000 are reinsured by a stop loss policy and are not paid for by the school district. Employee pharmacy data do not

include over-the-counter drugs, but only those medications requiring a prescription. In the United States, a drug is sold over-the-counter if the Food and Drug Administration deems it as sufficiently safe and effective. These medications are not included in the current study. Further, medical and pharmacy cost represents the amount paid by the insurance company as well as copays by the employee.

Statistical Techniques

Counts, means, standard deviations, medians, and percentages were used to describe the study population. Pair-wise comparisons of means were evaluated for statistical significance using the Student-Newman-Keuls Test. Risk ratios compare having a medical and pharmacy cost above the 50^{th} percentile (vs. below), 75^{th} percentile (vs. below), and 90^{th} percentile (vs. below). Statistical significance was determined by the corresponding 95% confidence intervals. For selected medications, the risk of medication use was compared using risk ratios and attributable fraction percentages across the levels of sex, age, and BMI weight classifications. Statistical significance of differences in percent use of selected medications across sex, age, and BMI categories was based on two-sided tests of significance were based on the 0.05 level against a null hypothesis of no association. Data was evaluated using the statistical software package PC-SAS (version 9.4; SAS Institute, Inc., 2014).

Results

In 2010-11, there were 3023 eligible employees, of which 2531 (83.72%) remained employed through the academic year 2013-14. Those more likely to remain employed over the study period were 40-59 years of age and had lower medical and pharmacy costs (Table 1). In 2010-11, ages

ranged from 18-76, with mean age significantly younger for those who remained employed (46.9 vs. 49.2, $p < 0.0001$). Those who stayed with the school district had significantly lower mean medical costs ($3056 vs. $7887, $p < 0.0001$) and mean pharmacy costs ($859 vs. $1105, p =0.0387). The results of this study are based on those continuously employed over the four academic years.

Most employees participated in annual wellness screening (84.1% in 2010-11, 84.4% in 2011-12, 87.6% in 2012-13, and 80.7% in 2013-14). In 2010-11, there was no significant difference in mean medical cost between those who participated in wellness screening and those who did not ($3148 vs. $2571, p = 0.2900). However, median medical cost was significantly greater for those who participated in wellness screening ($588 vs. $470, p = 0.0454). For all academic years, women were 1.03 (95% CI 1.01- 1.06) times more likely than men to complete annual wellness screenings, after adjusting for age and academic year. Participants in wellness screening were significantly younger (M = 47.8 vs. 49.8, $p < 0.0001$), after adjusting for sex and year. Those participating in wellness screening had significantly lower mean medical cost ($3093 vs. $4181, p = 0.0013), but experienced no significant difference in mean annual pharmacy costs, after adjusting for age, sex, and year.

Among participants in annual wellness screening, mean BMI remained constant across the academic years (Table 2). Mean BMI was greater for men than women and in ages 40 years and older. Medical and pharmacy costs were highly positively skewed, with considerable variability. Hence, identifying significant differences in the mean costs across the levels of sex, age, and year, were less likely to occur than to find significant differences in the median costs across the levels of these variables. Medical costs were higher for women than men, increased with age, and were greater in morbidly obese individuals. Pharmacy costs were higher in women than men, increased with age, and were lowest in those of normal weight.

The risk of medical and pharmacy costs above the 50th, 75th, and 90th percentiles are shown according to sex, age, and BMI weight classification in Table 3. Higher BMI has a greater impact on higher percentiles of medical and pharmacy costs. For example, morbidly obese compared with normal weight are 1.13 (13%), 1.30 (30%), and 1.93 (93%) more likely to have pharmacy costs above the 50th, 75th, and 90th percentiles, respectively. Medical and pharmacy costs above these percentiles are greater in women than men and increase with age.

Associations between selected percentiles of medical and pharmacy costs and BMI weight classifications varied according to age (Figure 1), but not sex (data not shown). Greater medical and pharmacy costs with older age groups are seen in the graph. However, the increasing costs with higher age are most pronounced in the underweight and morbidly obese groups.

Medication use is shown across sex, age, and BMI groups in Table 4. For any medication, women were 18% more likely to file a claim than men, employees 60 years of age or older were 23% more likely to file a claim than those less than 40 years, and morbidly obese were 6% more likely to file a claim than those of normal weight. For 22 of the 33 medications considered, the percentage of annual claims was higher for women than men. For high blood pressure and statins was the percentage of claims greater for men than women. For 25 of the medications, the percentage of annual claims increased with age. For 24 of the medications, the percentage of annual claims was associated with BMI (20 positively and 4 negatively). The strongest positive associations involved diabetes, high cholesterol (statins), blood thinners, high blood pressure, and edema. Negative associations involved acne, birth control, Herpes, and osteoporosis. The highest annual percent of acne, antibiotic, cold/influenza/allergy, and eye infection medications occurred in underweight individuals. For edema, muscle spasms, pain, and ulcers, medication use was comparatively high in underweight individuals, dropped for normal weight, and then increased in higher weight classifications.

We also report the attributable fraction in the population. For example, this statistic says that 8.82% of diabetes medication is attributed to being overweight, 20.34% is attributed to being obese, and 30.43% is attributed to being morbidly obese. Where the risk ratio is less than 1, the preventive fraction can be estimated. For example, the risk of requiring osteoporosis medication is lower for obese compared with normal weight employees (i.e., Risk Ratio = 0.54). The corresponding preventive fraction is 66%, meaning in the absence of obesity there would be 66% fewer claims for osteoporosis medication. The attributable fraction in the population and the preventive fraction both assume a cause-and-effect association between exposure and disease.

Discussion

The current study identified the degree to which sex, age, and BMI are associated with medical and pharmacy costs among employees in a large school district. Associations were also evaluated for 33 commonly prescribed medications.[28] The study extends previous research by including certain medications not previously evaluated and considering associations for all BMI weight classifications.

Higher medical and pharmacy costs among women, in older age, and among those not of normal weight is consistent with previous research.[8-10] Greater medical and pharmacy costs with older age are most pronounced in the underweight and morbidly obese groups. Hence, weight management at older ages appears particularly important in terms of lowering medical and pharmacy costs.

Higher medication use in women than men was primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Prescription costs for vitamins/minerals were also noticeably higher in women than men. Family planning and prenatal care may explain the greater use of birth control medications and vitamins/minerals among women. Loss of estrogen in women at older ages and female reproductive hormones may contribute to the higher level of osteoporosis and thyroid disease in women.[29 30]

Medication use was higher in those aged 60 years and older compared with those younger than 40, primarily because of diabetes, edema, high blood pressure, high cholesterol (statins), and thyroid disease. Previous research has shown that the risk of these diseases increase with age.[31-35] Medication use also noticeably increased with age for acid reflux, bowel/rectum, inflammation, and stomach acid. This is consistent with older age tending to be associated with more gastrointestinal problems.[36]

Medication use was highest in those who were morbidly obese. We found positive associations between body weight and higher use of medications for treating acid reflux, fungus, bacterial infections, arthritis, asthma, colds, influenza, allergies, depression, diabetes, edema, high blood pressure, muscle spasms, nausea/vomiting, pain, high cholesterol, stomach acid, thyroid, and ulcers. Other studies have identified a similar associations.[21 24 25 27] Morbidly obese individuals were also more likely to be prescribed vitamins and minerals than normal weight individuals. We did not find an association between body weight and increased use of medication for the bowel/rectum, skin, or urinary tract, which was counter to that found in other studies.[21 37-39] We also assessed but did not find a significant association for medications used to treat anxiety, insomnia, convulsions, or teeth and gums. The insignificant finding for anticonvulsants and teeth and gums may be because of insufficient power (i.e., small numbers). Finally, we assessed the association between body weight and medications for birth control, herpes, and osteoporosis, wherein significant negative associations were found. We are not aware of other studies that have looked at the association between body weight and medications used for colds, influenza, depression, edema, birth control, herpes, or osteoporosis.

Greater use of medication to treat acid reflux or stomach acid among individuals with higher BMI is consistent with previous research showing hospitalization rates for reflux disease to be positively associated with BMI.[40 41] Another study found that higher BMI was associated with increased gastroesophageal reflux in both normal and overweight individuals.[42] Heavier body weight can add pressure to the stomach and diaphragm, thereby resulting in reflux. Further, increased use of medication for nausea/vomiting among individuals with higher BMI weight classifications is consistent with other research.[43]

The positive association between higher BMI and increased use of medication for ulcers is consistent with other research, particularly peptic (gastric and duodenal) ulcers.[44 45] The mechanism to explain the association between obesity and peptic ulcer disease remains unclear. Obesity is also associated with Helicobacter pylori, which has been linked with gastric ulcers.[46]

Previous research has shown that overweight and obese individuals are at greater risk for infections.[37-49] This is consistent with our findings that show increased use of antibiotics and medication for acne, colds/influenza/allergy, and eye infections among obese individuals. However, it has been shown previously that antibiotics can also weaken the immune system,[50] as well as lead to obesity.[51] Some inflammatory diseases known to be associated with obesity in which we found a positive association between obesity and medication included influenza,[52 53] heart disease,[54] diabetes,[55] allergies,[56-59] asthma,[60] edema,[61-63] and arthritis.[64-67] A compromised immune system may also trigger autoimmune diseases, including rheumatoid arthritis and thyroid disease,[68] as indicated in the current study.

Overweight and obese individuals were more likely to receive cold, influenza, or allergy medication. Obesity is associated with impaired immune response to influenza vaccination in humans.[69] Because vaccination is less successful for obese individuals,[70 71] a greater level of medication may be sought for treating colds, influenza, and allergies.

Overweight and obese individuals received higher levels of pain medication. Research indicates that the nature of the relationship between higher BMI and pain is likely indirect.[72] For example, greater body weight is associated with osteoarthritis, which, in turn, leads to pain.[73] Being overweight or obese may result in greater risk for back pain, joint pain, and muscle spasms.[74] One study also found that obese individuals were more sensitive than those of normal weight to pressure pain.[75]

We found that higher BMI was associated with depression medication, as consistent with previous research.[76-79] In one study, the age-adjusted level of depression among adults (ages 20 and older) in the United States was 43.2% for those with depression compared with 33.0% for those without depression.[80] It may be that higher use of prescription medication for depression among those with greater BMI is partly because these people are more likely to experience other conditions related to depression, such as heart disease and diabetes.[81-83]

There was more use of vitamins/minerals among morbidly obese employees. Of the prescribed vitamins/minerals only 8.0% involved vitamin B and 57.3% involved vitamin D. A previous study showed an association between low vitamin B12 and being obese.[84] Another study found that the prevalence of vitamin D deficiency was 35% greater in obese individuals.[85]

Acne, antibiotic, cold/influenza/allergy, and eye infection medications were prescribed more often for underweight individuals. This is consistent with underweight individuals having poorer nutrition and, consequently, a weakened immune system.[86] For edema, muscle spasms, pain, and ulcers, medication use showed a J-shape relationship with BMI weight classification. Poor nutrition may also explain the higher levels of medication use among underweight individuals for these medications. Despite mean medical costs being similar for those who participated in wellness screening during the first year of the study, over the four academic years, participants in wellness screening ended up having significantly lower mean medical costs. However, pharmacy costs did not go down. It has been shown that wellness screening can cause the number and cost of pharmaceuticals to go up, at least initially, as the need for treatment is identified.[87] Identified treatment needs can then, in turn, help prevent more costly health problems in the future. For example, medications used to treat high blood pressure can result in lowering the risk of diabetes, heart disease, stroke and kidney disease; treatment of insomnia can help lower the risk of irritability, depression or anxiety, difficulty paying attention, and accidents due to increased errors; treatment of high cholesterol with statins can help lower the risk of cardiovascular disease; treatment of oral infections can help reduce the risk of diabetes, cardiovascular disease, and preterm birth; and vitamins/minerals can help prevent a host of diseases (scurvy, rickets, anemia, neural tube defects, pellagra, etc.). High blood pressure and statin medications were among the highest prescribed in our study.

A limitation of this study involves external validity (generalizability). Specifically, the study only considered those individuals who remained employed over all four academic years.

These people were generally healthier and in the age range 40-59. The study also focused on those who completed wellness screening because they contained BMI information. These employees were more likely women and younger. In addition, the causal direction between medication use and BMI could not be determined. That is, some medications may have contributed to body mass whereas others were in response to body mass. Finally, the current study did not have information on the use of vitamins or minerals obtained over the counter and small numbers made it impossible to evaluate the relationship between specific types of vitamins/minerals and sex, age, and BMI.

Conclusion

Weight management at older ages, particularly in underweight and morbidly obese individuals, is most important for lowering medical and pharmacy costs. Medical costs decreased, possibly because of effective drug treatment and prevention. Pharmacy costs remained constant, possibly because screening identified a need for certain medications. Greater use of medication among women than men is primarily because of drugs involving birth control, osteoporosis, thyroid disease, and urinary tract infection. Greater medication use in older age is primarily related to medications used to treat gastrointestinal problems. Medication use was positively associated with BMI for most of the conditions being treated, with exceptions involving birth control, herpes, and osteoporosis. A J-shape relationship between BMI weight classification and medication use for acne, antibiotic, cold/influenza/allergy, eye infection, edema, muscle spasms, pain, and ulcers may be because of poorer nutrition in underweight individuals.

References

1. 2016 Employer Health Benefits Survey. kff.org. http://www.kff.org/health-costs/report/2016-employer-health-benefits-survey/. Published September 14, 2016. Accessed February 21, 2018.

2. Chen L, Hannon PA, Laing SS, Kohn MJ, Clark K, Pritchard S, Harris JR. Perceived workplace health support is associated with employee productivity. Am J Health Promot. 2015;29(3):139-146.

3. Centers for Disease Control and Prevention. cdc.gov. http://www.cdc.gov/sustainability/worksitewellness/ Worksite wellness. Updated December 9, 2014. Accessed March 18, 2018.

4. Michaels CN, Greene AM. Worksite wellness: increasing adoption of workplace health promotion programs. Health Promot Pract. 2013;14(4):473-479.

5. Witt LB, Olsen D, Ablah E. Motivating factors for small and midsized businesses to implement worksite health promotion. Health Promot Pract. 2013;14(6), 876-884.

6. Niessen MA, Kraaijenhagen RA, Dijkgraaf MG, van Pelt D, van Kalken CK, Peek N. Impact of a Web-based worksite health promotion program on absenteeism. J Occup Environ Med. 2012;54(4):404-408.

7. Kaspin LC, Gorman KM, Miller RM. Systematic review of employer-sponsored wellness strategies and their economic and health-related outcomes. Popul Health Manag. 2013;16(1): 14-21.

8. Metge C, Black C, Peterson S, Kozyrskyi AL. The population's use of pharmaceuticals. Med Care. 1999;37(6 Suppl):JS42-JS59.

9. Bertakis K, Azari R, Helms L, Callahan E, Robbins J. Gender differences in the utilization of health care services. J Fam Pract. 2000;49(2):147-152.

10. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Int J Obes. 2005;29(3):334-339.

11. Karmali KN, Lloyd-Jones DM, Berendsen M, et al. Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. JAMA Cardiol. 2016;1(3):341-349.

12. Fretheim A, Odgaard-Jensen, Brørs O, Madsen S, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.

13. Taylor F, Huffman MD, Macedo A, et al. Statins for the primary prevention of cardiovascular disease. Cochrane. 2013. http://www.cochrane.org/CD004816/VASC_statins-primary-prevention-cardiovascular-disease. Accessed February 21, 2018.

14. Czeizel AE. Birth defects are preventable. Int J Med Sci. 2005;2(3):91-92.

15. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029-2043.

16. Asthma. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660. Published March 9, 2018. Accessed February 24, 2018.

17. Arthritis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/arthritis/diagnosis-treatment/drc-20350777. Published March 7, 2018. Accessed February 24, 2018.

18. Preventive Medicine Reports Paper

19. Thompson D, Edelsberg J, Colditz GA, Bird AP, Oster G. Lifetime health and economic consequences of obesity. Arch Intern Med. 1999;11;159(18):2177-2183.

20. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009;121(6):21-33.

21. Kinge JM, Morris S. Association between obesity and prescribed medication use in England. Econ Hum Biol. 2014;15:47-55.

22. Narbro K, Agren G, Jonsson E, et al. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. Arch Intern Med. 2002;162(18):2061-2069.

23. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff. 2009;28(5):w822-31.

24. Randhawa AK, Parikh JS, Kuk JL. Trends in medication use by body mass index and age between 1988 and 2012 in the United States. PLoS One. 2017 Sep 20;12(9):e0184089.

25. Kit BK, Ogden CL, Flegal KM. Prescription medication use among normal weight, overweight, and obese adults, United States, 2005-2008. Ann Epidemiol. 2012;22(2):112-119.

26. Jarrett B, Bloch GJ, Bennett D, Bleazard B, Hedges D. The influence of body mass index, age and gender on current illness: a cross-sectional study. Int J Obes. 2010;34(3):429-436.

27. Raebel MA, Malone DC, Conner DA, Xu S, Porter JA, Lanty FA. Health services use and health care costs of obese and nonobese individuals. Arch Intern Med. 2004;164(19):2135-2140.

28. Fuentes AV, Pineda MD, Venkata KCN. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. Pharmacy (Basel). 2018;6(2):E43.

29. Alswat KA. Gender disparities in osteoporosis. Clin Med Res. 2017;9(5): 382–387.

30. Li H, Li J. Thyroid disorders in women. Minerva Med. 2015;106(2):109-114.

31. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650-2664.

32. Trayes KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. Am Fam Physician. 2013;88(2):102-110.

33. Mc Donald Posso AJ, Motta Borrel JA, Fontes F, Cruz Gonzalez CE, Pachón Burgos AA, Cumbrera Ortega A. High blood pressure in Panama: Prevalence, sociodemographic and biologic profile, treatment, and control (STROBE). Medicine (Baltimore). 2014;93(22): e101.

34. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984-1994. Circulation. 1997;96(1):37-43.

35. Gesing A. The thyroid gland and the process of aging. Thyroid Res. 2015;8(Suppl 1):A8.

36. A L D'Souza. Ageing and the gut. Postgrad Med J. 2007; 83(975):44–53.

37. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916.

38. Brown J, Wimpenny P, Maughan H. Skin problems in people with obesity. Nurs Stand. 2004;18(35):38-42.

39. Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. Urology. 2012;79(2):266-269.

40. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup

Study. First National Health and Nutrition Examination Survey. Ann Epidemiol. 1999;9(7):424-435.

41. Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Alim Pharmacol Ther. 2013;37(5):555-563.
42. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Association between body mass index and gastroesophageal reflux symptoms in both normal weight and overweight women. N Engl J Med. 2006;354(22):2340-2348.
43. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol 2004;99(9):1807-1814.
44. Boylan MR, Khalili H, Huang ES, Chan AT. Measures of adiposity are associated with increased risk of peptic ulcer. Clin Gastroenterol Hepatol. 2014 Oct;12(10):1688-1694.
45. Kim J, Kim KH, Lee BJ. Association of peptic ulcer disease with obesity, nutritional components, and blood parameters in the Korean population. PLoS One. 2017;12(8): e0183777.
46. Xu M, Liu L, Yuan B, Yin J, Lu Q. Association of obesity with Helicobacter pylori infection: A retrospective study. World J Gastroenterol 2017;23(15):2750-2756.
47. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006;6(7)438-446.
48. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes. 2013;37:333-340.
49. Lübbeke A, Zingg M, Hoffmeyer P, et al. Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthopaedica. 2016;87(2):132-138

50. Yang JH, Bhargava P, McCloskey D, Mao N, Palsson BO, Collins JJ. Antibiotic-induced changes to the host metabolic environment inhibit drug efficacy and alter immune function. Cell Host & Mocrobe. 2017;22(6):757-765.

51. Early G. Current Evidence regarding antibiotic exposure and childhood obesity: an integrative review. Ped Nurs. 2017;43(4):169-174.

52. Bandaru P, Rajkimar H, Napanveettil G. The impact of obesity on immune response to infection and vaccine: an insight into plausible mechanisms. Endocrinol Metab Synd 2013;2:2.

53. Kwong JC, Campitelli MA, Rosella LC. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada: a cohort study. Clin Infect Dis. 2011;53(5):413-421.

54. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010;2010:535918.

55. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.

56. Ciprandi G, Pistorio A, Tosca M, Ferraro MR, Cirillo I. Body mass index, respiratory function and bronchial hyperactivity in allergic rhinitis and asthma. Respir Med 2009;103(2):289-295.

57. Gorgievska-Sukarovska B, Lipozencić J, Susac A. Obesity and allergic diseases. Acta Dermatovenerol Croat. 2008;16(4):231-235.

58. Shah R, Yang Y. Health and economic burden of obesity in elderly individuals with asthma in the United States. Popul Health Manag 2015;18(3):186-191.

59. Guo Y, Moon JY, Laurie CC, et al. Genetic Predisposition to Obesity is associated with Asthma in US Hispanics/Latinos: Results from the Hispanic Community Health Study/Study of Latinos. Allergy. 2018;doi: 10.1111/all.13450. [Epub ahead of print]

60. Rodriguez D. Obesity and Asthma – What's the Connection. https://www.everydayhealth.com/asthma/obesity-connection.aspx. Published August 28, 2013. Accessed April 12, 2018.

61. Greene, A.K., et al. Lower-Extremity Lymphedema and Elevated Body-Mass Index. N Engl J Med. 2012;366:2136-2137.

62. Helyer, L.K., et al. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. Breast J. 2012;16(1):48-54.

63. Greene AK, Grant FD, Slavin SA, Maclellan RA. Obesity-induced lymphedema: clinical and lymphoscintigraphic features. Plast Reconstr Surg. 2015;135(6):1715-1719.

64. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138(2):185-193.

65. Baodong Qin, Min Yang, Haitao Fu, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17(1):86.

66. Feng J, Chen Q, Yu F, et al. Body mass index and risk of rheumatoid arthritis: a meta-analysis of observational studies. Medicine. 2016;95(8):e2859.

67. Albrecht K, Richter A, Callhoff J, et al. Body mass index distribution in rheumatoid arthritis: a collaborative analysis from three large German rheumatoid arthritis databases. Arthritis Res Ther. 2016;18:149.

68. Rodriguez D. How Your Immune System Worsens Arthritis. EverydayHealth.com. https://www.everydayhealth.com/arthritis/understanding/the-immune-system.aspx. Published August 1, 2012. Accessed April 11, 2018.

69. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes. 2012;36(8):1072-1077.

70. Painter SD, Ovsyannikoa IG, Poland GA. The weight of obesity on the human immune response to vaccination. Vaccine. 2015;33(36): 4422–4429.

71. Young KM, Gray CM, Bekker LG. Is Obesity a Risk Factor for Vaccine Non-Responsiveness? PLoS One**.** 2013;8(12): e82779.

72. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8:399-408.

73. Erdmann J. Osteoarthritis and Obesity. www.arthritis.org. https://www.arthritis.org/living-with-arthritis/comorbidities/obesity-arthritis/osteoarthritis-and-obesity.php. Accessed April 11, 2018.

74. American Obesity Association. Health effects of obesity. AOA Fact Sheets. 2002.

75. Tashani OA, Asitita R, Sharp D, Johnson MI. Body mass index and distribution of body fat can influence sensory detection and pain sensitivity. Eur J Pain 2017;21(7):1186-1196.

76. Rathee N. Obesity and depression: Are they related? Indian J Health Well. 2017;8(12):1472-1475.

77. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. Int J Obesity. 2009;33(2):257-266.

78. Onyike CU, Crum RM, Lee HB, Lyketsos DG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003;158(12):1139-1147.

79. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2008;70(3):288-297.

80. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005-2010. NCHS Data Brief, No. 167, October 2014.

81. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry 2004;65(5):634-651.

82. Ferraro KF, Su Y, Gretebeck RJ, Black DR, Badylak SF. Body mass index and disability in adulthood: A 20-year panel study. Am J Public Health. 2002;92(5):834-840.

83. Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. J Psychosom Res. 2002;53(4):859-863.

84. Baltaci D, Kutlucan A, Turker Y, et al. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Med Glas. 2013;10(2):203-210.

85. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341-349.

86. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? The Lancet 2003;361:2226-2234.

87. Merrill RM, Telford CT. Pharmaceutical use according to participation in worksite wellness screening and health campaigns. Prev Med Rep 2018;12:158-163.

Footnotes

Contributors: RMM conceived and designed the epidemiological study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. RPF interpreted the data, provided a literature review, and revised the manuscript. Both authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by both authors.

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Patient and Public Involvement statement: Employee data consisted of sex, age, and BMI, which was linked to medical and pharmacy claims data. No personal identifying information was retained in the linked data set.

Table 1 Characterization of the study group according to sex, age, medical and pharmacy costs

			Continuously Employed			
	No.	%	%	Chi-square p value	Risk Ratio	95% CI
Sex						
Men	797	26.36	84.69	0.3884	1.00	
Women	2226	73.64	83.38		0.98	0.95-1.02
Age Group						
18-39	770	25.47	82.21	< 0.0001	1.00	
40-49	806	26.66	89.45		1.09	1.05-1.13
50-59	1088	35.99	88.24		1.07	1.03-1.12
60-76	359	11.88	60.45		0.74	0.67-0.80
Medical Cost (USD)						
0-184	755	25.0	87.55	< 0.0001	1.00	
185-604	757	25.0	85.07		0.97	0.93-1.01
605-2049	755	25.0	84.64		0.97	0.93-1.01
2050-7191	454	15.0	79.30		0.91	0.86-0.96
7192+	302	10.0	75.17		0.86	0.80-0.92
Pharmacy Cost (USD)						
0-6	759	25.0	86.92	< 0.0001	1.00	
7-194	755	25.0	85.21		0.99	0.69-1.03
195-903	755	25.0	82.59		0.96	0.92-1.00
904-2303	452	15.0	84.14		0.99	0.94-1.04
2304+	302	10.0	74.92		0.86	0.80-0.93

Sex, age, medical and pharmacy costs apply to the 2010-11 academic year.

Table 2 Medical and pharmacy costs according to sex, age, year, and body mass index

	BMI (kg/m²)			Medical Cost (USD)				Median one-way analysis	Pharmacy Cost (USD)				Median one-way analysis
	Mean	SD	SNK	Mean	SD	SNK	Median	p value	Mean	SD	SNK	Median	p value
Sex													
Men	29.35	5.80	A	2869	10581	A	373	< 0.0001	725	2324	A	53	< 0.0001
Women	27.26	6.47	B	3447	12049	A	741		963	3550	B	238	
Age Group													
18-39	27.17	6.06	A	2236	9344	A	389	< 0.0001	660	3342	A	70	< 0.0001
40-49	27.76	6.42	B	3052	12366	B	503		750	2806	A	106	
50-59	28.05	6.55	B	3935	12579	B	845		1021	3288	B	261	
60-76	28.17	6.13	B	3749	10831	B	989		1288	3990	C	344	
Year													
2010-11	27.89	6.40	A	3188	10524	A	605	0.2313	830	2247	A	195	0.0016
2011-12	27.79	6.31	A	3621	12816	A	610		953	3180	A	189	
2012-13	27.87	6.59	A	3208	11836	A	670		934	3571	A	173	
2013-14	27.63	6.16	A	3191	11557	A	651		894	3913	A	141	
BMI (kg/m²)													
Underweight				2191	1190	A	647	0.0003	1454	6706	A	224	0.0004
Normal weight				2826	333	A	650		779	3285	B	167	
Overweight				3174	514	A	603		926	3085	A, B	169	
Obese				3544	459	A	665		1031	3458	A, B	228	
Morbidly obese				6911	2092	B	1033		853	1493	A, B	242	

SNK: Student-Newman-Keuls Test. Different letters in the SNK columns indicate significant difference among the levels of the variables at the 0.05 level.

Table 3 Risk of medical and pharmacy costs (USD) above the 50th, 75th, and 90th percentiles according to BMI weight classification, sex, and age

	Medical						Pharmacy					
	50th percentile Above vs. below		75th percentile Above vs. below		90th percentile Above vs. below		50th percentile Above vs. below		75th percentile Above vs. below		90th percentile Above vs. below	
	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI
Sex												
Men	1.00		1.00		1.00		1.00		1.00		1.00	
Women	1.43	1.36-1.51	1.47	1.35-1.60	1.42	1.24-1.64	1.58	1.50-1.66	1.59	1.46-1.74	1.14	1.00-1.29
Age Groups												
18-39	1.00		1.00		1.00		1.00		1.00		1.00	
40-49	1.16	1.08-1.23	1.15	1.03-1.29	1.08	0.90-1.28	1.14	1.07-1.22	1.45	1.29-1.64	1.72	1.37-2.15
50-59	1.50	1.42-1.59	1.65	1.50-1.82	1.36	1.16-1.58	1.48	1.39-1.56	2.28	2.05-2.55	2.82	2.30-3.46
60+	1.61	1.52-1.72	1.83	1.64-2.04	1.33	1.11-1.60	1.57	1.48-1.68	2.57	2.29-2.89	3.78	3.06-4.68
BMI (kg/m^2)												
Underweight	1.05	0.88-1.26	0.91	0.64-1.31	0.61	0.28-1.35	2.05	1.25-3.34	1.05	0.74-1.48	2.05	1.25-3.34
Normal weight	1.00		1.00		1.00		1.00		1.00		1.00	
Overweight	0.95	0.90-1.00	0.95	0.86-1.05	1.01	0.85-1.20	1.01	0.95-1.06	1.18	1.07-1.30	1.68	1.41-2.00
Obese	1.00	0.95-1.06	1.14	1.03-1.25	1.21	1.01-1.43	1.11	1.05-1.17	1.19	1.08-1.31	1.76	1.47-2.12
Morbidly obese	1.18	1.08-1.29	1.62	1.40-1.87	2.18	1.72-2.77	1.13	1.03-1.25	1.30	1.09-1.55	1.93	1.43-2.61

Shaded cells represent statistical significance at the 0.05 level.

Table 4 Medication use according to sex, age, and BMI weight classification

		Sex		Age Group				Body Mass Index (kg/m^2)				
		Men	Women	18-39	40-49	50-59	60+	Underweight	Normal weight	Over weight	Obese	Morbidly obese
Medication	%											
Acid Reflux	5.75	5.56	5.81	3.02	4.54	7.14	8.36	3.57	4.34	5.36	7.19	9.14
Risk ratio		1.00	1.04	1.00	1.50	2.36	2.77	0.82	1.00	1.24	1.66	2.11
AF_p (%)		0.00	0.26	0.00	2.81	7.27	9.23		0.00	1.33	3.64	5.98
Acne	7.17	3.15	8.62	7.15	7.03	7.16	7.40	9.82	8.81	6.64	6.34	6.18
Risk ratio		1.00	2.74	1.00	0.98	1.00	1.03	1.11	1.00	0.75	0.72	0.70
AF_p (%)		0.00	11.07	0.00		0.01	0.25	0.82	0.00			
Antibiotic	21.21	17.81	22.44	18.72	20.76	22.76	21.93	25.89	20.54	20.74	23.73	21.24
Risk ratio		1.00	1.26	1.00	1.11	1.22	1.17	1.26	1.00	1.01	1.16	1.03
AF_p (%)		0.00	5.23	0.00	2.26	4.38	3.51	5.24	0.00	0.21	3.19	0.72
Anticonvulsants	1.49	1.39	1.53	1.84	1.32	1.45	1.40	2.68	1.25	1.13	1.65	1.61
Risk ratio		1.00	1.10	1.00	0.72	0.79	0.76	2.14	1.00	0.90	1.32	1.29
AF_p (%)		0.00	0.15	0.00				1.68	0.00		0.47	0.43
Antifungal	5.29	2.61	5.81	5.64	6.03	4.24	3.87	5.36	5.83	3.81	6.24	6.18
Risk ratio		1.00	2.23	1.00	1.07	0.75	0.69	0.92	1.00	0.65	1.07	1.06
AF_p (%)		0.00	6.09	0.00	0.36				0.00		0.37	0.32
Anxiety	7.88	6.31	8.45	6.42	7.80	8.36	8.97	8.93	7.22	7.11	7.29	6.45
Risk ratio		1.00	1.34	1.00	1.21	1.30	1.40	1.24	1.00	0.98	1.01	0.89
AF_p (%)		0.00	2.60	0.00	1.67	2.33	3.03	1.83	0.00		0.08	
Arthritis	11.06	11.13	11.03	7.72	10.53	12.83	12.56	7.14	9.36	10.72	13.84	14.78
Risk ratio		1.00	0.99	1.00	1.36	1.66	1.63	0.76	1.00	1.15	1.48	1.58
AF_p (%)		0.00		0.00	3.87	6.82	6.48		0.00	1.58	5.03	6.02
Asthma	8.61	7.19	9.13	7.48	8.80	8.00	11.22	6.25	6.24	8.74	10.39	10.75

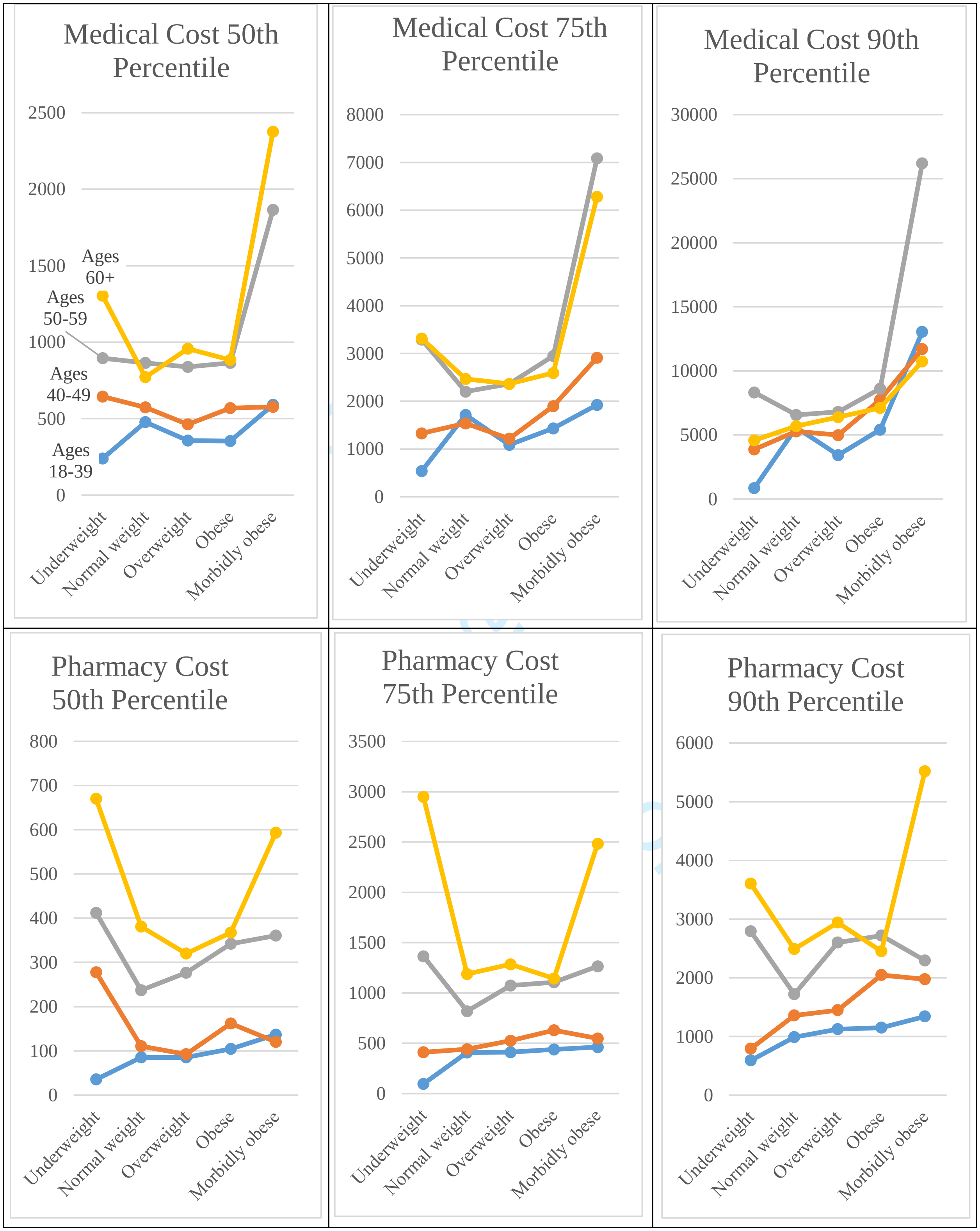
Risk ratio		1.00	1.27	1.00	1.18	1.07	1.50	1.00	1.00	1.40	1.67	1.72
AF_p (%)		0.00	2.27	0.00	1.50	0.59	4.13	0.01	0.00	3.33	5.42	5.86
Birth Control	8.71	0.24	10.88	21.13	8.77	2.59	0.95	10.71	11.69	7.30	6.34	6.99
Risk ratio		1.00	45.33	1.00	0.42	0.12	0.04	0.92	1.00	0.62	0.54	0.60
AF_p (%)		0.00	79.43	0.00					0.00			
Blood Thinner	1.26	1.85	1.05	3.91	18.75	45.31	32.03	0.95	0.52	1.15	2.08	5.22
Risk ratio		1.00	0.57	1.00	4.80	11.59	8.19	1.83	1.00	2.21	4.00	10.04
AF_p (%)		0.00		0	4.56	11.77	8.31	1.03	0	1.50	3.64	10.22
Bowel/Rectum	3.06	2.75	3.17	1.76	2.84	3.53	4.15	1.79	3.15	2.87	2.85	2.96
Risk ratio		1.00	1.15	1.00	1.61	2.01	2.36	0.57	1.00	0.91	0.90	0.94
AF_p (%)		0.00	0.47	0.00	1.84	2.99	3.99		0.00			
Cold/Influenza/Allergy	17.80	14.52	18.99	15.73	18.30	18.14	19.07	22.32	15.53	18.56	20.38	22.04
Risk ratio		1.00	1.31	1.00	1.16	1.15	1.21	1.44	1.00	1.20	1.31	1.42
AF_p (%)		0.00	5.20	0.00	2.83	2.65	3.64	7.22	0.00	3.36	5.27	6.94
Depression	18.24	10.28	21.14	12.51	19.30	20.75	18.84	15.18	16.20	17.59	20.83	18.55
Risk ratio		1.00	2.06	1.00	1.54	1.66	1.51	0.94	1.00	1.09	1.29	1.15
AF_p (%)		0.00	16.16	0.00	9.01	10.73	8.45		0.00	1.54	4.95	2.58
Diabetes	6.32	6.48	6.22	2.53	4.50	7.82	10.94	1.79	2.24	5.67	11.29	17.74
Risk ratio		1.00	0.96	1.00	1.78	3.09	4.32	0.80	1.00	2.53	5.04	7.92
AF_p (%)		0.00		0.00	4.69	11.67	17.36		0.00	8.82	20.34	30.43
Edema	5.14	3.12	5.87	2.04	3.64	6.48	8.86	6.25	3.08	4.66	7.29	12.90
Risk ratio		1.00	1.88	1.00	1.78	3.18	4.34	2.03	1.00	1.51	2.37	4.19
AF_p (%)		0.00	4.33	0.00	3.88	10.06	14.66	5.02	0.00	2.57	6.56	14.08
Eye Infection	12.01	9.23	12.87	11.44	13.06	11.13	12.34	14.29	11.02	12.12	13.64	9.68
Risk ratio		1.00	1.39	1.00	1.14	0.97	1.08	1.30	1.00	1.10	1.24	0.88
AF_p (%)		0.00	4.52	0.00	1.67		0.94	3.44	0.00	1.18	2.78	
Herpes	6.30	3.26	6.86	4.82	7.24	6.12	4.71	1.79	7.66	7.22	4.20	1.88
Risk ratio		1.00	2.10	1.00	1.50	1.27	0.98	0.23	1.00	0.94	0.55	0.25
AF_p (%)		0.00	6.50	0.00	3.07	1.67			0.00			
High Blood Pressure	16.49	19.95	15.60	4.58	11.05	22.78	29.39	6.25	8.54	17.44	24.68	31.99
Risk ratio		1.00	0.78	1.00	2.41	4.97	6.42	0.73	1.00	2.04	2.89	3.75
AF_p (%)		0.00		0.00	18.89	39.59	47.18		0.00	14.66	23.76	31.17

Inflammation	1.19	0.68	1.37	0.69	0.87	1.50	1.68	1.79	0.98	1.40	0.80	1.61
Risk ratio		1.00	2.01	1.00	1.26	2.17	2.43	1.83	1.00	1.43	0.82	1.64
AF_p (%)		0.00	1.19	0.00	0.31	1.38	1.68	0.97	0.00	0.51		0.76
Insomnia	4.23	2.24	4.95	2.70	3.60	5.72	4.04	8.93	4.07	3.92	3.85	4.84
Risk ratio		1.00	2.21	1.00	1.33	2.12	1.50	2.19	1.00	0.96	0.95	1.19
AF_p (%)		0.00	4.87	0.00	1.39	4.52	2.06	4.81	0.00			0.79
Muscle Spasms	4.34	3.53	4.64	3.11	4.57	4.93	4.37	5.36	3.29	4.27	5.44	6.99
Risk ratio		1.00	1.31	1.00	1.47	1.59	1.41	1.63	1.00	1.30	1.65	2.12
AF_p (%)		0.00	1.35	0.00	2.00	2.48	1.73	2.66	0.00	1.28	2.76	4.65
Nausea/Vomiting	5.01	3.77	5.47	5.44	4.85	4.83	5.10	4.46	4.14	4.50	6.19	5.65
Risk ratio		1.00	1.45	1.00	0.89	0.89	0.94	1.08	1.00	1.09	1.50	1.36
AF_p (%)		0.00	2.21	0.00				0.39	0.00	0.43	2.42	1.79
Opioids	17.04	15.98	17.42	14.14	16.29	18.62	18.73	17.86	13.39	15.77	20.28	27.69
Risk ratio		1.00	1.09	1.00	1.15	1.32	1.32	1.33	1.00	1.18	1.51	2.07
AF_p (%)		0.00	1.51	0.00	2.53	5.12	5.24	5.38	0.00	2.94	8.06	15.40
Osteoporosis	1.21	0.07	1.63	0.00	0.17	1.30	4.37	0.89	1.56	1.20	0.85	0.00
Risk ratio		1.00	23.29	1.00				0.57	1.00	0.77	0.54	0.00
AF_p (%)		0.00	21.24	0.00					0.00			
Pain – non opioid	2.19	1.63	2.39	2.78	2.15	1.98	1.91	3.57	1.73	1.67	2.55	2.96
Risk ratio		1.00	1.47	1.00	0.77	0.71	0.69	2.06	1.00	0.97	1.47	1.71
AF_p (%)		0.00	1.01	0.00				2.28	0.00		1.03	1.53
Skin	6.84	4.88	7.55	5.44	6.44	7.37	8.24	6.25	7.25	6.41	7.19	5.38
Risk ratio		1.00	1.55	1.00	1.18	1.35	1.51	0.86	1.00	0.88	0.99	0.74
AF_p (%)		0.00	3.61	0.00	1.24	2.37	3.40		0.00			
Statins	14.49	17.93	13.24	2.31	8.53	20.58	28.4	3.81	7.02	17.95	19.89	27.47
Risk ratio		1.00	0.74	1.00	3.69	8.91	12.29	0.54	1.00	2.56	2.83	3.91
AF_p (%)		0.00		0.00	28.07	53.40	62.07		0.00	18.41	20.99	29.68
Stomach Acid	1.19	1.49	1.07	0.86	1.25	0.99	1.96	0.89	0.81	1.01	1.90	1.08
Risk ratio		1.00	0.72	1.00	1.45	1.15	2.28	1.10	1.00	1.25	2.35	1.33
AF_p (%)		0.00		0.00	0.54	0.18	1.50	0.12	0.00	0.29	1.58	0.40
Teeth/Gums	0.43	0.37	0.46	0.37	0.35	0.43	0.67	0.00	0.27	0.43	0.35	0.27
Risk ratio		1.00	1.24	1.00	0.95	1.16	1.81	0.00	1.00	1.59	1.30	1.00

AF_p (%)		0.00	0.10	0.00		0.07	0.35		0.00	0.25	0.13	0.00
Thyroid	12.76	2.99	16.31	4.37	11.19	16.92	17.61	6.25	13.97	12.74	13.94	19.09
Risk ratio		1.00	5.45	1.00	2.56	3.87	4.03	0.45	1.00	0.91	1.00	1.37
AF_p (%)		0.00	36.24	0.00	16.61	26.82	27.88		0.00			4.47
Ulcers	9.38	8.55	9.69	8.30	8.28	10.19	10.88	10.71	7.59	9.90	10.99	15.32
Risk ratio		1.00	1.13	1.00	1.00	1.23	1.31	1.41	1.00	1.30	1.45	2.02
AF_p (%)		0.00	1.24	0.00		2.09	2.83	3.71	0.00	2.78	4.03	8.72
Urinary Tract Infection	3.01	0.20	4.44	3.39	3.08	3.45	3.25	6.25	3.83	2.83	3.50	3.76
Risk ratio		1.00	22.20	1.00	0.91	1.02	0.96	1.63	1.00	0.74	0.91	0.98
AF_p (%)		0.00	38.95	0.00		0.05		1.87	0.00			
Vitamins/Minerals	2.07	0.71	2.57	2.49	1.73	1.88	2.47	0.00	2.07	1.28	1.75	5.38
Risk ratio		1.00	3.62	1.00	0.69	0.76	0.99	0.00	1.00	0.62	0.85	2.60
AF_p (%)		0.00	5.14	0.00					0.00			3.20
All prescriptions	80.87	71.40	84.32	71.52	78.45	85.24	88.00	83.93	81.46	81.28	83.47	86.29
Risk ratio		1.00	1.18	1.00	1.10	1.19	1.23	1.03	1.00	1.00	1.02	1.06
AF_p (%)		0.00	12.77	0.00	7.27	13.43	15.71	2.39	0.00		1.96	4.58

AF_p: Attributable fraction in the population. Shaded cells represent statistical significance at the 0.05 level. Cells that are left blank had a negative AF_p. In these cases the preventive fraction ([Risk Ratio – 1] × 100) is more appropriate.

Figure 1. Median medical and pharmacy cost (USD) according to Body Mass Index weight classifications and age


Medical Cost 50th Percentile
2500
2000
1500
1000
500
0
Ages 60+
Ages 50-59
Ages 40-49
Ages 18-39
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Medical Cost 75th Percentile
8000
7000
6000
5000
4000
3000
2000
1000
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Medical Cost 90th Percentile
30000
25000
20000
15000
10000
5000
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Pharmacy Cost 50th Percentile
800
700
600
500
400
300
200
100
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Pharmacy Cost 75th Percentile
3500
3000
2500
2000
1500
1000
500
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese
Pharmacy Cost 90th Percentile
6000
5000
4000
3000
2000
1000
0
Underweight
Normal weight
Overweight
Obese
Morbidly obese

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page/line numbers
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1/6, 2/25
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Done
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Done
Objectives	3	State specific objectives, including any prespecified hypotheses	Done
Methods			
Study design	4	Present key elements of study design early in the paper	Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Done
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Done
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	Done
Bias	9	Describe any efforts to address potential sources of bias	Done
Study size	10	Explain how the study size was arrived at	Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Done
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
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	Done
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Done
		(b) Indicate number of participants with missing data for each variable of interest	Done
		(c) Summarise follow-up time (eg, average and total amount)	Done
Outcome data	15*	Report numbers of outcome events or summary measures over time	Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Done

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Done
Discussion			
Key results	18	Summarise key results with reference to study objectives	Done
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	Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done
Generalisability	21	Discuss the generalisability (external validity) of the study results	Done
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	Done

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.