Incident gout and weight change patterns: a retrospective cohort study of US adults

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Abstract

OBJECTIVE

To investigated the association between weight change patterns across adulthood and incident gout.

METHODS

Using data from the National Health and Nutrition Examination Survey (NHANES), we categorized individuals into four weight-change groups based on their recalled weight during young adulthood and midlife. Hazard ratios (HR) and 95% CI relating weight change patterns to incident gout over 10-year follow-up were calculated. The hypothetical population attributable fraction (PAF) for the weight change patterns was calculated.

RESULTS

Among our sample of adults who were 40–74 years old at their midlife weight measure (n = 11079), 320 developed to gout. Compared with participants who remained stable non-obese during adulthood, the highest risks were found for gaining weight (HR 1.65; 1.19–2.29) participants. And stable obese pattern had a marginal significance of the elevated risk of incident gout conditions (HR 1.84; 0.98–2.78). No significant associations were found between losing weight change patterns and the risk of gout during the study period. If participants who gained weight had become non-obese during the 10-year follow-up, an estimated 3.2%(95% CI: 0-6.3) of observed gout cases could have been averted. Also, if the population had maintained a normal BMI, 32.9%(95% CI: 18.2–44.9) of cases could have been prevented during the ten years.

CONCLUSIONS

Gaining weight over adulthood was associated with increased risks of gout. These findings highlight that maintaining non-obese weight and weight loss across adulthood is essential for the prevention and treatment of gout in adult life.

Introduction

Gout is a common form of inflammatory arthritis[1]; the overall prevalence of gout among US adults was 3.9%. Characterized by monosodium urate (MSU) crystal deposition resulting from chronic elevation of serum uric acid (SUA)[2], gout can lead to severe arthropathies, physical impairment, and a decreased quality of life. The general management principle is to reduce SUA levels, allowing MSU crystals to dissolve, leading to the elimination of acute attacks and possible cure of the disease[3]. The worldwide

prevalence of gout is on an upward trend, with increasing obesity being a significant risk factor for gout development in a large epidemiological study. Gout also affected by numerous factors, including sugar-sweetened beverages(SSB), alcohol consumption, renal disease, and the use of diuretics and antihypertensive drugs[], a meta-analysis published recently indicated that SSB consumption was significantly associated with increased risk of gout in the adult population. Obesity is a major global health challenge. The association between obesity and gout might be attributed to insulin resistance, which in turn reduces renal urate excretion resulting in hyperuricemia. The American College of Rheumatology guidelines recommends weight loss as part of gout management for patients with obesity.

Although some prospective studies have clarified a relationship between obesity and incidence of gout[][], how the weight change during the transition from early adulthood to midlife and different weight change patterns in specific age ranges influence the incidence of gout in later life remains unknown.

We treated a national probability sample as a retrospective longitudinal study of using national data from NHANES 2007–2014 by a particular application. These data provided a chance to test a hypothesis about the association between weight change from young adulthood to midlife and risk of incident gout. We hypothesize that individuals who were obese or gaining weight were at an increased risk of gout relative to individuals who maintained a non-obese BMI over time (“residual risk” hypothesis). After testing the hypothesis, we speculated our findings to estimate the percentage of incident gout cases that could be averted under hypothetical scenarios related to weight change across young adulthood and midlife.

Research Design And Methods

Data Sources

Data for this study were drawn from NHANES 2007–2014, a continuous cross-sectional survey of the non-institutionalized civilian US population conducted in 2-year cycles. Interviews were conducted at individuals’ homes, and laboratory and physical examinations were performed by trained technicians using mobile examination centers. NHANES methods and protocols (including participant consent) have been described extensively. Self-reported weight change was assessed by participant recall of weight at age 25 and 10 years before the NHANES survey. We investigated the association between weight change and the risk of incident gout over the ten years from the midlife measure to the time of the survey. The study design is visually depicted in Fig. 1. The NHANES studies underwent institutional review board approval, and written informed consent was obtained from participants before starting the study.

Weight Change Measures

Data on weight at age 25 and at ten years before the NHANES survey were recalled. In this case, BMI at age 25 was calculated by the reported height at age 25, which we considered young adulthood. Likewise,

we regarded the recalled weight ten years before the survey as a measure of midlife weight. We used measured height at the survey to calculate BMI at midlife. BMI at age 25 (BMI_{25}) and ten years before the survey ($BMI_{10prior)}$ was calculated as weight (kg) divided by the square of height (m2). BMI change patterns, according to the BMI change track, were categorized by four groups from BMI_{25} to $BMI_{10\ prior}$. The criteria are as follows[1]: Stable non-obese: $BMI_{25} < 30\ kg/m^2$ and $BMI_{10\ prior} < 30\ kg/m^2$; losing: $BMI_{25} \geq 30\ kg/m^2$ and $BMI_{10\ prior} < 30\ kg/m^2$; gaining: $BMI_{25} < 30\ kg/m^2$ and $BMI_{10\ prior} \geq 30\ kg/m^2$; stable obese: $BMI_{25} \geq 30\ kg/m^2$ and $BMI_{10\ prior} \geq 30\ kg/m^2$.

Assessment of incident gout

Participants were considered as current gout if they reported being told that a health care provider had indicated a diagnosis of gout at the survey (gout incidence during follow-up was created based on the information on gout diagnosis and the use of gout medications).

Statistics

Tests of statistical significance were two-tailed, with a level of 0.05. STATA15.0 was used to perform all analyses. All analyses were performed with SUDAAN (SUDAAN Language Manual, Release 9.0, 2004; Research Triangle Institute, North Carolina, USA), which takes into account the complex sampling design used in NHANES yielding unbiased standard error estimates[23]. Percentages of missing values of covariates were less than 5% except for income (6.8%). We compared baseline characteristics by weight change patterns by using the $\chi 2$ test for categorical variables and analysis of variance adjusted for sampling weights for continuous variables.

In the second analysis, multiple logistic regression models were performed to examine the association between weight change patterns and corresponding 95% confidence intervals for incident gout. We hypothesize that individuals who were obese or gaining to an obese weight had an increased risk of gout relative to individuals who maintained a non-obese BMI over time (“residual risk” hypothesis). To test this “residual risk” hypothesis, the stable non-obese weight change patterns were used as the reference category to which all other weight change patterns were compared. Models included adjustment for ethnicity, sex, age, current smoke (yes/no), annual household income, diabetes, hypertension, and alcoholic drinks.

Hypothetical Scenarios

In the third part of the analysis, we calculated the hypothetical population attributable fraction (PAF) for the weight change patterns, an estimation of the percentage of prevalent gout in the study population that theoretically would not have occurred if all people had been relevant weight change patterns, assuming a causal relation. To allow valid calculation of PAF, logistic regression models with covariates were included in the model. For these analyses, we used a single binary categorical variable and compared participants in the weight change pattern with the rest of the population to calculate the population attributable fraction in total population and relevant individuals.

Under the first scenario, we estimated what would have happened if those who were gaining weight to a non-obese BMI at age 25 and during midlife. Under the second scenario, we calculated the proportion of averted cases if those who had a stable obese BMI during the period had a non-obese weight; Then, under the third scenario, we examined the percentage of the entire population if those who had a normal BMI at age 25 and during midlife.

Results

Clinical features of participants

Clinical characteristics for participants according to the weight-change category, are shown in Table 1.

Overall, 11079 participants were available for research. In terms of weight change, 7945 (71.7%) of the population was in a stable non-obese group, 115 (1.0%) reported losing from an obese BMI to a non-obese BMI, 2307 (20.8%) reported gaining weight, and 712 (6.5%) remained stable obese between young adulthood to midlife. A medical history of hypertension ranged from 33.2% among those who sustained non-obese to 57.1% among those who gained BMI. The history of diabetes was 6.8% of those who maintained non-obese and 25.9% of those who keep obese BMI.

Regarding weight change, 71.7% of the population was stable non-obese, 1.0% reported losing from an obese BMI to a non-obese BMI, 20.8% reported gaining weight, and 6.5% remained stable obese between young adulthood and midlife.

Different weight change patterns had a different prevalence of comorbidities, such as diabetes mellitus (6.8% in stable non-obese group, 15.8% in losing group, 24.6% in gaining group, and 25.9% in the stable obese group), and hypertension (33.2% in stable non-obese group, 41.8% in losing group, 57.1% in gaining group, and 56.5% in the stable obese group).

Association of weight change pattern and incident gout

Compared with stable non-obese individuals, those who gained weight from young adulthood through midlife had the highest risk (HR 1.65; 95% CI 1.19, 2.29) of developing gout during the ten years of follow-up (Table 2) and those who reported sustained an obese BMI from early adulthood to midlife had 1.84 (95% CI 0.98, 2.78) times the risk of developing gout. No significant difference (HR 0.48; 95% CI 0.09, 2.61) was observed in the risk of onset gout between those reporting losing from an obese BMI to a non-obese BMI over the period.

Cumulative incident gout defined by the onset of the recent ten years according to the obesity track.

Figure 2 illustrates cumulative incidence curves by time in study for each weight change group. Cumulative incidence of onset gout were 1.96% (95% CI, 1.58%,2.43%) for sustained non-obese, 0.87% (95% CI, 0.15%,4.74%) for losing, 4.19% (95% CI, 3.31%, 5.28%) for gaining, and 4.12% (95% CI, 2.53%, 6.63%) for stable obese.

Population attributable fractions for population counterfactuals of incident gout among weight change patterns

Three scenarios that are defined in the RESEARCH DESIGN AND METHODS were to calculate population attributable fractions (Table 3). In the first scenario, if those who were gaining weight to a non-obese BMI, 11.5% (95% CI 4.6, 17.9) of observed gout cases could have been averted (Table 3). In the second scenario, if those who kept an obese BMI during the period had a non-obese weight, 3.2% (95% CI 0, 6,3) of the observed cases would have been averted. In the third scenario, maintaining a normal BMI between young adulthood and midlife of the total population would have prevented 32.9% (95% CI 18.2, 44.9) of gout cases.

Discussion

In this large prospective study of nationally representative US adults, the highest incidence of gout was in stable obese participants. While maintained non-obese weight was beneficial compared with being stable obese from early to midlife, those who gained weight from early to midlife were significantly related to increased incidence of gout risk. Also, these results emphasize the importance of maintaining non-obese weight across adulthood, especially weight loss for obese individuals whenever from early adulthood to midlife, for reducing gout risk in later life.

Comparison between previous studies and our results

A study conducted in China found that those who had a weight gain of 5kg, 20 kg or higher from early to midlife was associated with a high risk of gout for both woman and man[25]. A systematic review and meta-analysis found in obese individuals, gout was 2.24 times more likely to occur than normal weight[26]. A population-based cohort study indicated obese individuals have an adjusted 2.4-fold higher risk of developing gout than a non-obese individual during nine-year follow-up[20]. These findings support the results from our study that hazard ratios of gout were 1.65 for gaining individuals and 1.84 for stable obese individuals during ten-year. The cumulative incidence of gout at age 70 was 11.8% with BMI ≥35 kg/m2, compared with only 1.9% in those with BMI <25 kg/m[26 27]. Similar results are observed in our study stratified by weight changes patterns from age 25 to 10-year prior the survey, with cumulative incidence curves by time in study for each weight change group, 1.96% (1.58%,2.43%) for sustained non-obese, 0.87% (0.15%,4.74%) for losing, 4.19% (3.31%, 5.28%) for gaining, and 4.12% (2.53%, 6.63%) for stable obese (Figure1). In a national-level survey, the prevalence of abdominal obesity was higher for gouty than non-gouty patients, at 62.9% (95% CI, 50.9–74.8) versus 35.3% (95% CI, 33.7–36.9) [28]. Additionally, the risk of gout increases with obesity[29].

Not only the relationship of the obesity status at a single time point and risk of gout should be focused on, but also the relationship of changes in body weight and risk of gout, for weight changes are common across adulthood. While in individuals with gout, especially during adulthood, studies about the

cumulative effects of obesity on gout are rare. Our study has the unique feature of examining the weight change patterns from early to midlife and gout risk in later life.

Obesity is associated with a dose-dependent increase in the RRs of incident gout[30], suggesting gout incidence could be lessened by interventions aiming at obesity. The part of hypothetical scenarios targeted to explore the prevention initiatives for weight gain and the potential effect of weight-loss interventions. In the scenario of preventing weight gain in the population after age 25 and maintaining a non-obese BMI, 11.5% (95% CI 4.6, 17.9) reduction in gout cases in the population would happen. If all those who were obese at age 25 lost to a non-obese BMI by midlife, 3.2% (95% CI 0, 6.3) of observed incident gout could be averted. Likewise, we found that 32.9% (95% CI 18.2, 44.9) of gout cases during this period could be averted if all individuals in the population maintained a normal weight from early adulthood to midlife. Our hypothetical scenarios are consistent with previous studies that examined the effect of weight change on gout. Studies on the effects of weight-loss interventions from either bariatric surgery or lifestyle modification are associated with reduced incidence of gout[28,31,32,33]. A systematic review[34]shows that a weight loss of >3.5 kg showed beneficial effects on gout attacks at medium-term/long-term follow-up.

However, in our study, the losing group has a wide 95% CI because weight loss from an obese BMI to a non-obese BMI was rare, only accounting for 1.0% of the total population.

Potential mechanisms

The pathogenesis of gout is due to high SUA levels resulting in the formation of MSU crystals[35], which then contributes to an inflammatory response with tissue damage[3637]. Although the majority of people with hyperuricemia do not have gout, increased SUA levels still raise the risk of developing gout[38]. Several studies have demonstrated a strong association between gout, SUA levels, obesity, and metabolic syndrome, including hypertension, dyslipidemia[22,39,40]. The paper by Lyndgoh et al.[41] indicates that raised SUA is an outcome but not a cause of obesity. This has been assumed to be contributed to high SUA levels causing impaired nitric oxide production, endothelial dysfunction, enhanced oxidative stress, and maladaptive immune and inflammatory responses[42]. Obesity, and in particular abdominal obesity, has been associated with hyperuricemia, possibly due to increasing production and reduced renal excretion of urate[43-44]. Weight gain has been associated with increasing SUA levels in some studies[45,46]and other studies found that weight loss reduced the level of SUA[47-48].

Strengths and limitation

Our study has several strengths and limitations. Among the former is the validation of findings in a large, nationally representative cohort of the US, which estimate the relationship of weight change across the early adulthood to midlife and incident gout over the ten years from the midlife measure to the time of the survey. Another is to explore the effect of different weight change patterns from early adulthood to midlife, which incorporates both the weight track and life periods, to predict the difference in the effect of

weight change in certain life periods on the development of gout. This study also has several limitations. First, weight at early adulthood was recalled at a later age; some misclassifications of weight change were inevitable. Second, the definition of gout in epidemiological studies vary and includes, either in isolation or combination, physician-diagnosed gout based on history and examination, prescription practices, and analysis of health care datasets or coding systems. We believe the self-reporting of medically diagnosed gout is a real definition for epidemiological purposes which is supported by a 2011 US study explicitly addressing the question of reliability and sensitivity of self-reported physician-diagnosed gout[49]. Using a large cohort consisting of more than 32000 participants, this group found that self-reported physician-diagnosed gout was consistent both over multiple questionnaires and with the duration of time. They found a sensitivity of 84% compared against the gold standard, defined as a hospital discharge diagnosis of gout or use of gout-specific medications (colchicine, probenicid, allopurinol).

Conclusion And Public Health Implications

NHANES survey data were analyzed by a novel application to explore the relationship of weight change patterns to incident gout over the early adulthood to midlife. Regarding residual risk hypothesis, those who were stable obese had a higher risk of incident gout than those who remained non-obese throughout the life span. Our hypothetical scenarios indicated beneficial effects of positive weight intervention change from either stable obese or gaining weight to sustained normal, from stable obese to weight loss. Taken together, the findings support the advantage of maintaining normal weight over the whole of adulthood would be beneficial to reducing the risk of gout among obese individuals. The significance of developing policies and programs that reduce the prevalence of obesity is underscored by our results from a national sample. Identifying populations at risk of developing gout may provide opportunities for primary prevention. Clinical trials on the long-term health consequences of weight intervention are warranted.

Abbreviations

BMI: body mass index; SUA: serum uric acid; PAF: population attributable fraction; HR: Hazard ratios; NHANES: National Health and Nutritional Examination Survey;

Declarations

Ethics approval and consent to participate

The NHANES studies underwent institutional review board approval, and written informed consent was obtained from participants before starting the study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Availability of data and materials

Data from the National Health and Nutritional Examination Survey are available online through the CDC.

Competing interests

All authors declare that they have no conflict of interest.

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Authors' contributions

JBZ contributed to studying the concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. LB, YJW, and MAC drafted the manuscript, and all authors read and approved the final manuscript.

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References

1 Smith EU, Díaz-Torné C, Perez-Ruiz F, March L M. Epidemiology of gout: an update. Best Pract Res Clin Rheumatol 2010;24:811–27.

2 Gurkirpal Singh, Bharathi Lingala, Alka Mithal. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology 2019;58:2177-80.

3 Dalbeth N, Fransen J, Jansen TL, Neogi T, Schumacher HR, Taylor WJ. New classification criteria for gout: a framework for progress. Rheumatology 2013;52:1748–53.

4 Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. Gout classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74:1789–98.

5 Scire CA, Manara M, Cimmino MA, Govoni M, Salaffi F, Punzi L, et al. Gout impacts on function and health-related quality of life beyond associated risk factors and medical conditions: results from the KING observational study of the Italian Society for Rheumatology (SIR) Arthritis. Res Ther 2013;15: R101.

6 Bernal JA, Quilis N, Andrés M, Sivera F, Pascual E. Gout: optimizing treatment to achieve a disease cure. Ther Adv Chronic Dis 2016;7:135–44.

7 Grassi D, Pontremoli R, Bocale R, Ferri C, Desideri G. Therapeutic approaches to chronic hyperuricemia and gout. High Blood Press Cardiovasc Prev 2014;21:243–50.

8 Kiltz U, Smolen J, Bardin T, Cohen SA, Dalbeth N, Doherty M, et al. Treat-to-target (T2T) recommendations for gout. Ann Rheum Dis 2016;76:1-7.

9 Roddy E, Choi HK. Epidemiology of gout. Rheum Dis Clin North Am 2014;40:155-75.

10 Delbeth N, Merriman TR, Stamp LK. Gout. The Lancet 2016;388:2039-52.

11 Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence,incidence and risk factors. Nat Rev Rheumatol 2015;11:649-62.

12 Rai SK, Fung TT, Lu N, Keller SF, Curhan GC, Choi HK. The dietary approaches to stop hypertension (DASH) diet, western diet, and risk of gout in men: prospective cohort study. BMJ 2017;357:j1794.

13 Ebrahimpour-Koujan S; Saneei P; Larijani B, Esmaillzadeh A. Consumption of sugar sweetened beverages and dietary fructose in relation to risk of gout and hyperuricemia: a systematic review and meta-analysis. Crit Rev Food Sci Nutr 2020 ;60:1-10.

14 World Health Organization. Obesity. http://www.who.int/gho/ncd/risk_factors/obesity _text/en/. Accessed August 14, 2016.

15 Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, Gans RO. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. Clin Sci (Lond) 1997;92:51–8.

16 Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431-46.

17 Bhole V, de Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of gout in women: fifty-two-year follow-up of a prospective cohort. Arthritis Rheum 2010;62:1069-76.

18 Cea Soriano L, Rothenbacher D, Choi HK, Garcia Rodriguez LA. Contemporary epidemiology of gout in the UK general population. Arthritis Res Ther 2011;13:R39.

19 Maynard JW, McAdams DeMarco MA, Baer AN, Kottgen A, Folsom AR,Coresh J, et al. Incident gout in women and association with obesity in the atherosclerosis risk in communities (ARIC) study. Am J Med 2012;125:717.e9-717.e17.

20 McAdams-DeMarco MA, Maynard JW, Baer AN, Coresh J. Hypertension and the risk of incident gout in a population-based study: the atherosclerosis risk in communities cohort. J Clin Hypertens (Greenwich) 2012;14:675-79.

21 Chen JH, Pan WH, Hsu CC, Yeh WT, Chuang SY, Chen PY, et al.

Impact of obesity and hypertriglyceridemia on gout development with or without hyperuricemia: a prospective study. Arthritis Care Res (Hoboken) 2013;65:133-40.

22 Centers for Disease Control and Prevention (CDC). About the National Health and Nutrition Examination Survey. 2017 https://www.cdc.gov/nchs/nhanes/about_nhanes.htm

23 Yuan Y. Multiple imputation using SAS software. J StatSoftw 2011;45:1-25.

24 Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 1994;140:303-09.

25 Guochong Jia, Xiao-Ou Shu, Ying Liu, Honglan Li, Hui Cai ,Jing Gao,

et al. Association of Adult Weight Gain With Major Health Outcomes Among Middle-aged Chinese Persons With Low Body Weight in Early Adulthood. JAMA Network Open. 2019;2:e1917371.

26 Peter LE, James AP, John B, Christian DM,Charles AH, Edward R. Obesity, hypertension and diuretic use as risk factors for incident gout: a systematic review and meta-analysis of cohort studies. Arthritis Research & Therapy 2018; 20:1301-11.

27 Puig JG, Martinez MA. Hyperuricemia, gout and the metabolic syndrome. Curr. Opin. Rheumatol 2008; 20:187-91.

28 Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2007;57:109–15.

29 Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165:742–8.

30 Dagfifinn A, Teresa N, Lars JV. Body mass index and the risk of gout: a systematic review and dose–response meta-analysis of prospective studies. Eur J Nutr 2014; 53:1591-601.

31 Dalbeth N, Chen P, White M, Gamble GD,Barratt-Boyes C, Gow PJ, et al. Impact of bariatric surgery on serum urate targets in people with morbid obesity and diabetes: a prospective longitudinal study. Ann Rheum Dis 2014;73:797–802.

32 Dessein PH, Shipton EA, Stanwix AE, Joffe BI,Ramokgadi J. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. Ann Rheum Dis 2000;59:539–43.

33 Maglio C, Peltonen M, Neovius M, Jacobson P, Jacobsson L, Rudin A, Carlsson LM. Effects of bariatric surgery on gout incidence in the Swedish Obese Subjects study: a non-randomised, prospective, controlled intervention trial. Ann Rheum Dis 2016;76:688–93.

34 Nielsen SM, Bartels EM,Henriksen M, Wæhrens EE, Gudbergsen H, Bliddal H. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. Ann Rheum Dis 2017; 76:1870-82.

35 McGill NW. The epidemiology and treatment of gout. Open access rheumatology: research and reviews 2011;3:73-82.

36 Cleophas MC, Crisan TO, Joosten LA. Factors modulating the inflammatory response in acute gouty arthritis. Curr Opin Rheumatol 2017;29:163-70.

37 Joosten LA, Netea MG, Mylona E, Koenders MI, Malireddi RK, Oosting M, et al. Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1beta production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. Arthritis Rheum 2010;62:3237-48.

38 Shiozawa A, Szabo SM, Bolzani A, Cheung A, Choi HK. Serum uric acid and the risk of incident and recurrent gout: a systematic review. J Rheumatol 2017;44:388-96.

39 Heinig M, Johnson RJ. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve Clin J Med 2006;73:1059-64.

40 Soltani Z, Rasheed K, Kapusta DR, Reisin E. Potential role of uric acid in metabolic syndrome, hypertension, kidney injury, and cardiovascular diseases: is it time for reappraisal? Curr Hypertens Rep 2013;15:175-81.

41 Lyngdoh T, Vuistiner P, Marques-Vidal P, Rousson V, Waeber Gérard,Vollenweider P, et al. Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. PLoS ONE 2012;7:e39321.

42 Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric acid—key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal medicine 2013;3:208-20.

43 Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. Metabolism 1998; 47:929-33.

44 Gao B, Zhou J, Ge J,Zhang YP, Chen F, Lau WB, et al. Association of maximum weight with hyperuricemia risk: a retrospective study of 21,414 Chinese people. PLoS ONE 2012; 7:e51186.

45 Glynn RJ, Campion EW, Silbert JE. Trends in serum uric acid levels 1961–1980. Arthritis Rheum 1983; 26:87–93.

46 Villegas R, Xiang YB, Cai QY, Fazio S, Linton MR,Li HL, et al. Prevalence and determinants of hyperuricemia in middle-aged, urban Chinese men. Metab Syndr Relat Disord 2010; 8:263-70.

47 Yamashita S, Matsuzawa Y, Tokunaga K, Fujioka S, Tarui S. Studies on the impaired metabolism of uric acid in obese subjects: marked reduction of renal urate excretion and its improvement by a low-calorie diet. Int J Obes 1986;10:255-64.

48 Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. Rheumatology (Oxford) 2010; 49:2391-99.

49 McAdams M, Maynard J, Baer A, Kottgen A, Clip S, Coresh J et al. Reliability and sensitivity of the selfreport of physician-diagnosed gout in the campaign against cancer and heart disease and the atherosclerosis risk in the community cohorts. J Rheumatol 2011; 38: 135-41

Tables

Table 1. Characteristics at survey of weight change patterns from age 25 to 10 years before survey in adults ages 40-74* (N=11079)

	Stable non-obese	Losing body weight	Gaining body weight	Stable obese
No of participates, n(%)	7,945(71.7)	115(1.0)	2,307(20.8)	712(6.5)
Age (years),	54.1(53.7,54.4)	52.0(50.6,53.5)	56.8(56.2,57.4)	51.3(50.4,52.1)
Female, n (%)	4,082(53.0)	49(45.5)	1,198(49.9)	368(46.6)
Black, n (%)	1,699 (9.9)	27(16.2)	578 (11.6)	239(17.3)
Current smoke, n (%)	1,799(21.1)	39(34.9)	386(16.4)	150(18.3)
Alcoholic drinks, average day	1.6(1.6,1.7)	2.1(1.5,2.8)	1.4(1.3,1.5)	1.7(1.4,2.0)
Diabetes, n(%)	793 (6.8)	22(15.8)	684 (24.6)	217(25.9)
Hypertension, n(%)	2,978(33.2)	48(41.8)	1,392(57.1)	419(56.5)
Annual household income ≥65000$, n (%)	2,644(47.8)	29(32.1)	671(41.4)	187(38.4)
BMI, mean (95%CI), kg/m2				
At 25years age[a]	22.1(22.0,22.2)	34.5(33.1,35.9)	24.9(24.7,25.1)	34.7(34.1,35.2)
At 10 years prior[b]	24.6(24.5,24.7)	26.7(26.0,27.4)	34.2(34.0,34.5)	39.0(38.2,39.9)
At examination[c]	26.9 (26.7,27.0)	30.5(28.9,32.1)	34.8(34.5,35.1)	39.3(38.5,40.2)

* NHANES (2007–2014); sample weighted estimates.

aSelf-reported BMI 25 years age. bSelf-reported BMI 10 years before examination. cSelf-reported BMI at examination.

Table 2. HRs for weight change pattern and incident gout*

Obesity track	HR†	95% CI	P value
Stable obese	1.84	(0.98-2.78)	0.02
Gaining weight	1.65	(1.19-2.29)	0.003
Losing weight	0.48	(0.09-2.61)	0.39
Stable non-obese	reference	1.0	

*NHANES, National Health and Nutrition Examination Survey (2007-2014).

†Adjusted for ethnicity, sex, age, current smoke (yes/no), annual household income, diabetes, hypertension, and alcoholic drinks.

Table 3. Population attributable fractions (PAF) for population counterfactuals of incident gout among weight change patterns across adulthood*

Scenario†	PAF (%)95%CI -total population	PAF(%)95%CI -subpopulation
1 From gaining to sustained non-obese	11.5(4.6,17.9)	36.4(18.6,50.3)
2 From sustained obese to sustained non-obese	3.2(0,6.3)	37.6(6.0,58.7)
3 Total population to sustained normal	32.9(18.2,44.9)	42.8(25.8,55.9)

*Source: NHANES (2007–2014). †Adjusted for ethnicity, sex, age, current smoke (yes/no), annual household income,diabetes, hypertension, and alcoholic drinks.

From younger age to later, 1: If those who gained weight, instead remained non-obese 2. If those who maintained an obese BMI, instead lost to a non-obese BMI; 3. If the total population had a normal BMI from young adulthood that was maintained through midlife.

Figures

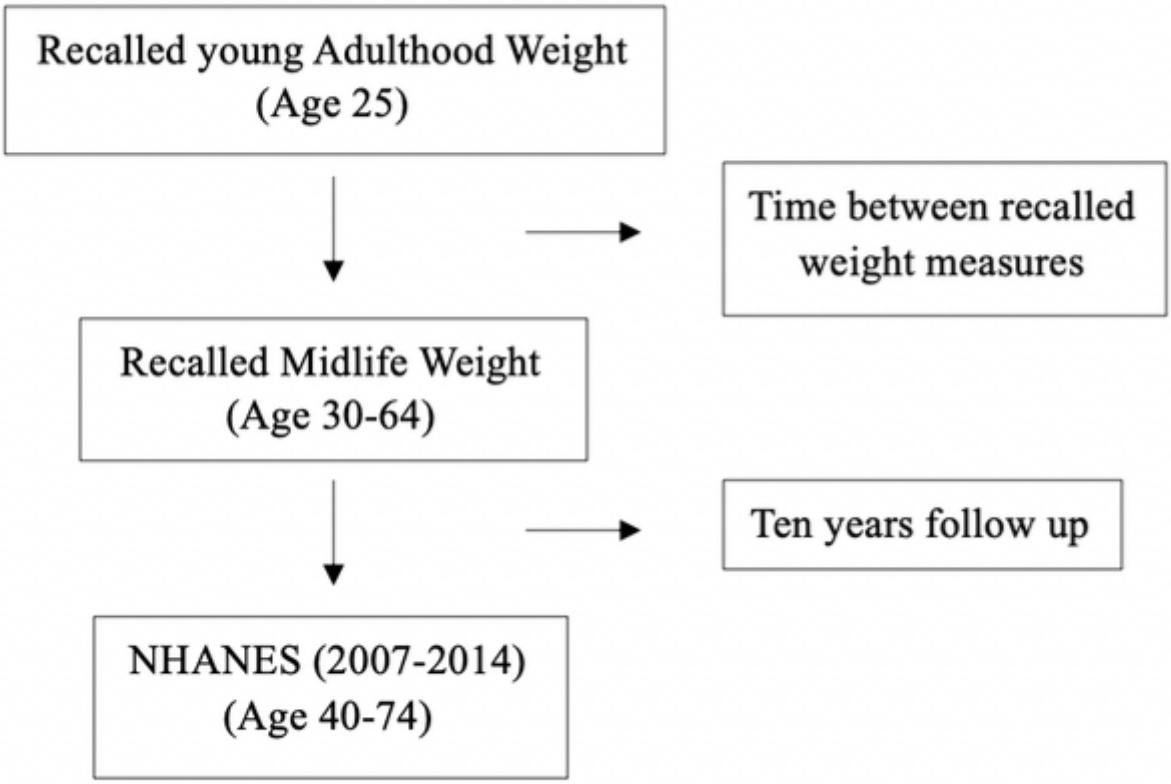

Figure 1

Study design for analysis of incident gout (n= 11079). It shows how a cross-sectional, retrospective cohort of US adults were created. We studied individuals who participated in the NHANES (2007-2014) cross-sectional survey at ages 40-74 years. It based on participants' recalled weight history at age 25 (young adulthood) and ten years before the survey (age 30-64 years, midlife), which were used to create a measure of weight change between young adulthood and midlife. We then investigated the association between this weight change and the successive risk of developing into gout. 'Follow-up' for incident gout began at ten years before the survey. Individuals who reported receiving a first diagnosis of gout between ten years before the survey and time of the survey were considered to have experienced incident gout.

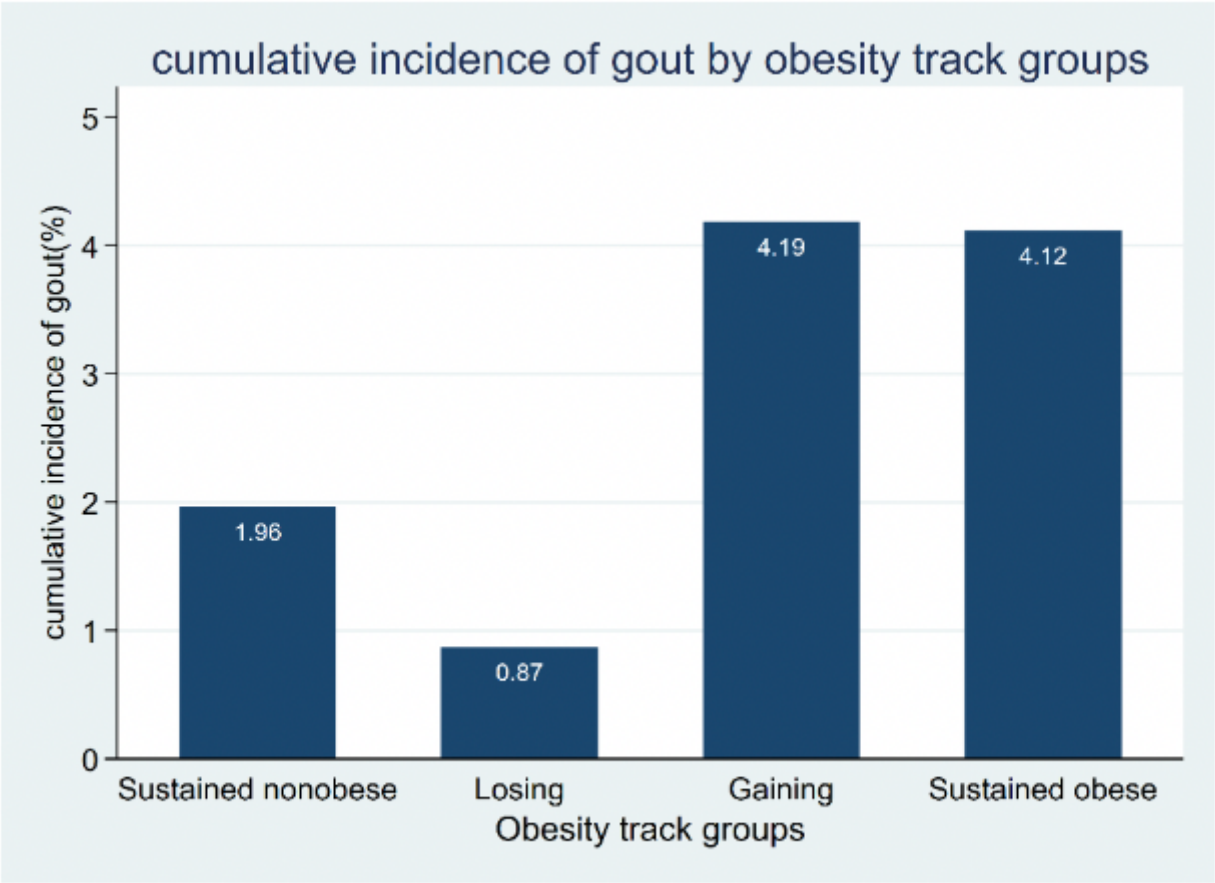

Figure 2

Cumulative incident gout defined by onset of recent ten years according to obesity track. Obesity duration over adulthood was based on obesity status from age 25 to examination and categorized as follows: 1) Stable non-obese: BMI25 <30 kg/m2 and BMI10 prior <30kg/m2; 2) losing BMI25≥30kg/m2 and BMI10 prior<30kg/m2; 3) gaining: BMI25 <30kg/m2 and BMI10 prior ≥30kg/m2 ; and 4) stable obese: BMI25 ≥30kg/m2 and BMI10 prior≥30kg/m2. Cumulative incident gout recent ten years was based on onset of gout from ten years prior to examination to examination.