ARTICLE

Prescribing semaglutide for weight loss in non-diabetic, obese patients is associated with an increased risk of erectile dysfunction: a TriNetX database study

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Semaglutide was approved in June 2021 for weight loss in non-diabetic, obese patients. While package inserts include sexual dysfunction as a side effect, no study has assessed the degree of this risk. The objective of our study is to assess the risk of developing erectile dysfunction after semaglutide is prescribed for weight loss in obese, non-diabetic men. The TriNetX Research database was used to identify men without a diagnosis of diabetes ages 18 to 50 with BMI > 30 who were prescribed semaglutide after June 1st, 2021. Men were excluded if they had a prior erectile dysfunction diagnosis, any phosphodiesterase-5 inhibitors prescription, intracavernosal injections, penile prosthesis placement, history of testosterone deficiency, testosterone prescription, pelvic radiation, radical prostatectomy, pulmonary hypertension, or were deceased. We further restricted our cohort to non-diabetic, obese men by excluding men with a prior diabetes mellitus diagnosis, a hemoglobin A1c > 6.5%, or having ever received insulin or metformin. Men were then stratified into cohorts of those that did and did not receive a semaglutide prescription. The primary outcome was the risk of new ED diagnosis and/or new prescription of phosphodiesterase type 5 inhibitors at least one month after prescription of semaglutide. The secondary outcome was risk of testosterone deficiency diagnosis. Risk was reported using risk ratios with 95% confidence intervals (95% CI). 3,094 non-diabetic, obese men ages 18–50 who received a prescription of semaglutide were identified and subsequently matched to an equal number cohort of non-diabetic, obese men who never received a prescription of semaglutide. After matching, average age at index prescription for non-diabetic, obese men was 37.8 ± 7.8 and average BMI at index prescription was 38.6 ± 5.6. Non-diabetic men prescribed semaglutide were significantly more likely to develop erectile dysfunction and/or were prescribed phosphodiesterase type 5 inhibitors (1.47% vs 0.32%; RR: 4.5; 95% CI [2.3, 9.0]) and testosterone deficiency (1.53% vs 0.80%; RR: 1.9; 95% CI [1.2, 3.1]) when compared to the control cohort of non-diabetic men who never received a semaglutide prescription.

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INTRODUCTION

Semaglutide's approval by the FDA in 2021 represents a pivotal advancement in treating obesity [1]. This injectable medication has been highly effective for weight loss [2]. The recognition of its potential has marked a paradigm shift in obesity therapeutics, offering new hope for individuals grappling with weight-related health concerns. More recently semaglutide has been found to decrease the risk of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal strokes in obese men and women without diabetes [3].

However, every medication comes with its own set of considerations and semaglutide is no exception. Understanding the side effect profile of this medication, particularly its impact on sexual health, is vital for comprehensive patient care [4]. Sexual dysfunction, a side effect mentioned on the package inserts, merits specific attention due to its influence on the quality of life and well-being of individuals [5]. Despite the inclusion of sexual dysfunction as a known side effect, it has yet to be characterized on a large scale.

As semaglutide gains traction for its role in weight loss, a nuanced exploration of its known side effects becomes imperative. Against this backdrop, our study aims to address a gap in semaglutide's side effect profile. Specifically, we aim to investigate the risk of erectile dysfunction (ED) and testosterone deficiency in a large population of non-diabetic men prescribed semaglutide for weight loss. Due to the expected weight loss, we predicted that the rates of ED and testosterone deficiency would be lower after administration of the medication. By elucidating the nuances of sexual dysfunction as a potential side effect of semaglutide, we strive to empower healthcare providers with knowledge that can inform personalized patient care.

METHODS

Data source and study design

Data used in this study was collected and analyzed in December 2023 from the TriNetX, LLC Research Network, which provided access to electronic

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medical records and insurance claims for approximately 118 million patients from 81 healthcare organizations [6]. Data from TriNetX includes included information on demographics, diagnoses, procedures, prescriptions, and laboratory values. Diagnoses were recorded using International Classification of Disease (ICD) codes, procedures were recorded using Current Procedural Terminology (CPT) codes, and laboratory tests were identified via Logical Observation Identifiers Names and Codes (LOINC). Information on medications was obtained from prescriptions, orders, inpatient medication reconciliations, and charted medications and were identified in the database using Veterans Affairs (VA) Drug classification system. The data used in the study covered the period from June 2021 through December 2023.

The process by which the data was de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)[1] of the HIPAA Privacy Rule. Because studies using TriNetX de-identified patient records do not involve the collection, use, or transmittal of individually identifiable data, the qualified expert has determined these studies are exempted from need of Institutional Review Board. Any patient counts less than 10 are obfuscated to ensure patient anonymity and only aggregate patient counts and statistical summaries are provided.

Cohorts

Within the database, we identified men ages 18 to 50 prescribed semaglutide after June 1st, 2021 with a body mass index (BMI) > 30. Men were excluded if they had a prior history of ED (ICD10 N52), any phosphodiesterase-5 inhibitors (PDE5i) use (RxNorm 1291301, 136411, 306674, or 358263), intracavernosal injections (CPT 54235), penile prosthesis placement (CPT 54405-8, 54410-11, 54415-17), history of testosterone deficiency (ICD10 E29.1), testosterone prescription (RxNorm 10379), pelvic radiation (ICD10 D7YFZZ, D7Y7, D707), radical prostatectomy (CPT 1014183), pulmonary hypertension (ICD10 I27.2, I27.20, I27.89, I27.0), or were deceased. We further restricted our cohort to non-diabetic, obese men by excluding men with a history of diabetes mellitus (ICD E08-13), a hemoglobin A1c > 6.5%, or having ever received insulin (VA HS501) or metformin (RxNorm 6809). Men were then stratified into cohorts of those that did and did not receive a semaglutide prescription (RxNorm 1991302).

The primary outcome of interest was the new diagnosis of ED and/or prescription of PDE5i (sildenafil, tadalafil only 10 or 20 mg doses, vardenafil, or avanafil) at least one month after the index prescription of semaglutide. The secondary outcome was the risk of new testosterone deficiency (ICD10 E29.1) diagnosis after semaglutide prescription. An internal null-sensitivity analysis was performed using a benign prostatic hyperplasia diagnosis (ICD10 N40) which was not expected to be impacted.

Statistical analysis

The entirety of the analysis was performed on TriNetX platform. Chi square test and *T* test were used for univariate analysis. 1:1 propensity score matching was performed with age (continuous variable), race/ethnicity, BMI (TNX Curated 9083), tobacco use (ICD10 Z72.0), alcohol use (ICD10 F10), hypertension (ICD10 I10), sleep apnea (ICD10 G47.3), and hyperlipidemia (ICD10 E78.5) as covariates. These variables were chosen as they are established risk factors for ED and testosterone deficiency or were significantly different between the 2 cohorts. For each patient in the smaller cohort, the system chooses a 1:1 match from the larger cohort based on the propensity scores generated by using greedy nearest neighbor algorithms utilizing a caliper width of 0.1 times pooled standard deviations. Balance on covariates was assessed using standardized mean difference and absolute values > 0.1 were considered positive for residual imbalance. The order of records is randomized to eliminate bias using a fixed seed during matching, allowing for reproducibility. A two-sided alpha of less than 0.05 was defined as a priori for statistical significance. The TriNetX Platform calculates risk ratios (RR) and associated 95% confidence intervals (95% CI), using R's Survival package, version 3.2-3 (R Group for Statistical Computing).

Details of propensity score matching: TriNetX platform utilizes input matrices of user-identified covariates and conducts logistic regression analysis to obtain propensity scores for individual subjects [6]. 1:1 matching was performed based on the propensity scores generated by using greedy nearest neighbor algorithms utilizing a caliper width of 0.1 times pooled standard deviations (SD). TriNetX randomizes the order of rows in order to eliminate bias resulting from nearest-neighbor algorithms. This method has been used in published studies preceding this analysis [7, 8].

RESULTS

We identified 3094 non-diabetic, obese men ages 18–50 who received a prescription of semaglutide and were subsequently matched to an equal number cohort consisting of non-diabetic, obese men who never received a prescription of semaglutide (Table 1). After matching, the average age of men was 37.8 in both cohorts and the majority of men were white (74%). After matching, the average age at index prescription was 37.8 ± 7.77 for the non-diabetic, obese men cohort and was 37.8 ± 8.10 for the matched controls. Only BMI at the time of the index prescription differed significantly between the two groups with a BMI of 38.7 ± 5.6 kg/m^2 for the men prescribed semaglutide versus 37.2 ± 6.0 kg/m^2 for the cohort of men that were not, p < 0.0001.

Table 1. Propensity score-matching analysis matching for age, race/ethnicity, BMI, tobacco use, alcohol use, hypertension, sleep apnea, and hyperlipidemia.

	Prior to propensity match			After propensity match		
	Semaglutide	**Matched Controls**	**P value***	**Semaglutide**	**Matched Controls**	**P value***
Included Males	3,095	462,555		3,094	3,094	
White	73.51%	61.35%	**<0.0001**	73.5%	73.6%	0.908
Black	9.34%	15.28%	**<0.0001**	9.3%	10.8%	0.052
Unknown Race	6.75%	7.99%	**<0.0001**	6.8%	6.0%	0.915
Hispanic or Latino	12.05%	15.25%	**<0.0001**	12.1%	10.7%	0.093
Not Hispanic or Latino	80.23%	69.74%	**<0.0001**	80.2%	82.3%	0.054
Unknown Ethnicity	7.72%	15.02%	**<0.0001**	7.7%	7.0%	0.263
Average Age at Index Prescription	37.8 ± 7.77	37.8 ± 8.10	**<0.0001**	37.8 ± 7.77	37.8 ± 8.10	0.849
Body Mass Index	38.65 ± 5.62	38.65 ± 5.62	**<0.0001**	38.65 ± 5.62	37.15 ± 6.01	**<0.0001**
Sleep Apnea	36.32%	6.45%	**<0.0001**	36.3%	35.4%	0.474
Hyperlipidemia	21.81%	5.45%	**<0.0001**	21.8%	20.9%	0.385
Hypertension	38.55%	11.70%	**<0.0001**	38.5%	40.2%	0.176
Alcohol Use Disorder	3.97%	3.13%	**<0.0001**	4.0%	4.3%	0.523
Tobacco Use	2.33%	1.97%	**0.155**	2.3%	2.7%	0.331

*p value after unpaired t test performed with a significance set at a > 0.05. Significant lab values are displayed in bold.

1.47% of the non-diabetic, obese men prescribed semaglutide were diagnosed with ED or were prescribed PDE5i compared to 0.32% of the men in the matched control group (RR 4.5, 95% CI 2.3-9.0). 1.53% of the non-diabetic, obese men were diagnosed with testosterone deficiency after prescription of semaglutide compared to 0.80% of men in the matched control group (RR: 1.9; 95% CI [1.2, 3.1]). There was no significant difference between the two cohorts in rates of benign prostatic hyperplasia diagnosis (0.55% vs 0.71%; RR: 0.8; 95% CI [0.4, 1.5]) after the index semaglutide prescription. Figure 1 displays the results of this study.

DISCUSSION

Our study finds a significant increased risk of diagnoses of both ED and testosterone deficiency in men aged 18–50 who were prescribed semaglutide when compared with matched controls. It is important to note that the rates of ED and testosterone deficiency in men receiving semaglutide are low, 1.47%, which may be acceptable risk for patients given the potential weight-loss and cardiac benefits [3]. Herein, we define the risk of these diagnoses and do note a statistically increased risk for obese, non-diabetic men compared to obese, non-diabetic men not receiving semaglutide. In the analysis we sought to target the impact of this drug by excluding men over the age of 50, given greater risk of developing ED with older ages, and excluding those with diabetes mellitus and matched cardiovascular risk factors, which are known contributors to both ED and hypogonadism [9, 10]. After excluding and matching for potential confounding factors, we found that our results contradicted our initial hypothesis that receiving a prescription semaglutide for weight loss and cardiovascular health would decrease the risk of ED and testosterone deficiency and, thus, warrant further discussion [11, 12].

Obesity is estimated to affect over 35% of US adults with increasing rates [13]. The prevalence of ED in obese men is high, ranging from 13.0 to 42.1% [14–17]. Excess body weight is strongly associated abnormal sex hormone levels, microvascular dysfunction, and chronic systemic inflammation [18, 19]. Low testosterone and high estradiol levels are common in obese males due to the increased expression of aromatase in the visceral adipose tissue, leading to secondary hypogonadism [20]. By losing excess body fat, hormonal levels would be expected to revert to the norm, but the association with testosterone deficiency as seen in our study raises concern of an unexplained physiologic interaction encountered by administration of semaglutide.

Unfortunately, the effects of semaglutide on sexual function have not yet been thoroughly investigated, as the popular medication was only approved for the use in diabetics in 2017 However, early studies display a significant cardiovascular benefit of semaglutide, which ordinarily decreases the risk of ED [3]. On the other hand, within the same trials, there was a reported increased risk of metabolic disorders which may have overlapping side effects of low testosterone [3]. Possible explanations for ED and testosterone deficiency include potential interactions with Leydig cells which express the glucagon like peptide-1 receptor and regulate glucagon like peptide-1 secretion, decreased pulsatile testosterone secretion, and direct smooth muscle relaxation by stimulation of glucagon like peptide-1 receptor present in the cavernosal tissue similar to the delayed functioning of the gastrointestinal tract [21–24]. However, as there is scant research investigating the sexual side effects of semaglutide, all current explanations are purely speculation that necessitate further exploration in basic science research and clinical trials.

Given these results, clinicians can now better inform patients who may have questions regarding the prevalence of sexual dysfunction listed on the package insert and prophylactically monitor sexual health after prescribing semaglutide to maximize patient adherence. While long-term weight loss may outweigh any underlying biochemical pathway impacting men's health, sexual dysfunction side effects are a known deterrent of critical medications, such as anti-hypertensives and anti-depressants [25]. Thus, providers should investigate sexual health in patients on semaglutide to maximize the benefit and treat underlying deterring factors that may lead to self-discontinuation.

Our study faces inherent limitations common to claims-based database research, encompassing challenges associated with

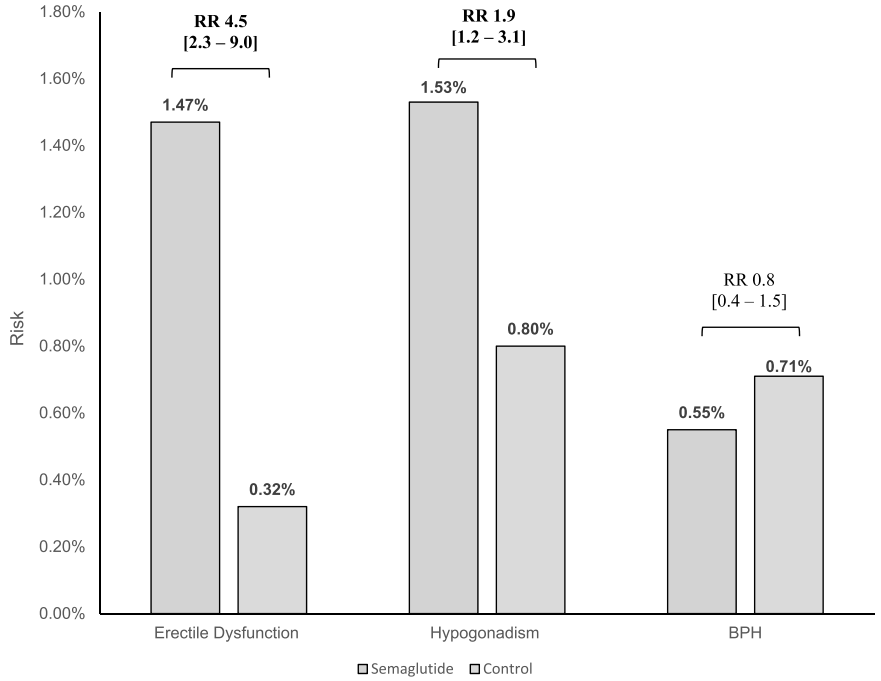

Fig. 1 Results of the analysis comparing men prescribed semaglutide to the control cohort of men not prescribed semaglutide after propensity score-matching for age, race/ethnicity, BMI, tobacco use, alcohol use, hypertension, sleep apnea, and hyperlipidemia. RR risk ratio, 95% CI = 95% Confidence Interval.

reliance on accurate ICD-10 and pharmaceutical classification and the absence of reliable adherence data. The potential of skewed outcome rates due to patients lost to follow-up cannot be ignored. Specifically, our inclusion criteria are limited to men prescribed semaglutide after June 1st, 2021, resulting in restricted follow-up time from the index prescription. Therefore, we cannot be sure about whether semaglutide is a predictor of these disorders or the effects on sexual health and function over the long-term. Additionally, we can only confirm that semaglutide was prescribed but do not know if the medication was actually administered. We additionally do not know the nature of sexual dysfunction, whether impaired libido or inability to achieve and maintain an erection—these will need to be determined in upcoming clinic-based analyses. Lastly, despite our attempts to provide a matched control cohort for comparison, the average BMI at the time of the index prescription was statistically different (38.7 ± 5.6 kg/m^2 for men receiving a semaglutide prescription versus 37.2 ± 6.0 kg/m^2 those not receiving a semaglutide prescription). While not entirely clinically significant with a mean difference of 1.5 kg/m^2, this lends to speculation of our findings, as this may create cohorts of men with more significant health conditions, potentially skewing the data to demonstrate a relationship that is not truly significant in a cohort in which BMI is able to be better matched. The BMI of the two cohorts could in part be explained by the underlying reason for prescription, uncontrolled obesity, which may demonstrate worse overall health. While this study provides the preliminary basis for sexual function in a new, popular medication, further studies investigating changes in testosterone, libido, and erectile function will need to be performed to provide validation of our findings.

Despite these challenges, the utilization of TriNetX Research database provides substantial strengths with its ability to leverage a vast network encompassing over 118 million patients from 81 healthcare organizations. The extensive database ensures robust statistical power and allows for national-level generalizability. Linking individual identifiers to pharmaceutical data and insurance claims within electronic health records enhances data comprehensiveness. Additionally, the use of specific ICD-10 and CPT codes have been previously validated for similar analyses, which minimizes selection bias and increases the reliability of our analysis [26].

CONCLUSION

Although the overall incidence of developing ED and testosterone deficiency was low in these younger men, we found that non-diabetic, obese males prescribed semaglutide were at an increased risk, despite the known impact on weight loss after starting the medication. Men that are prescribed semaglutide for weight loss and cardiovascular risk should be counseled on this potential risk factor prior to initiating therapy, especially those at higher risk. Further research must be performed to understand possible underlying biologic pathways that result in sexual dysfunction side effects to maximize the benefit of this popular medication and increase patient adherence.

REFERENCES

1. Commissioner O of the. FDA. FDA; 2021. [cited 2024 Feb 4]. FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014
2. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA. 2021;325:1414.
3. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. New Engl J Med. 2023;0:null.
4. Smits MM, Van Raalte DH. Safety of semaglutide. Front Endocrinol (Lausanne). 2021;12:645563.
5. Elterman DS, Bhattacharyya SK, Mafilios M, Woodward E, Nitschelm K, Burnett AL. The quality of life and economic burden of erectile dysfunction. Res Rep Urol. 2021;13:79–86.
6. Hadi YB, Lakhani DA, Naqvi SF, Fatima NU, Sarwari AR. Outcomes of SARS-CoV-2 infection in patients with cystic fibrosis: a multicenter retrospective research network study. Respir Med. 2021;188:106606.
7. Agrawal P, Singh SM, Able C, Kohn TP, Herati AS. Sleep disorders are associated with testosterone deficiency and erectile dysfunction—a U.S. claims database analysis. Int J Impot Res. 2024;36:78–82.
8. Nackeeran S, Havanur A, Ory J, Althof S, Ramasamy R. Erectile dysfunction is a modifiable risk factor for major depressive disorder: analysis of a federated research network. J Sexual Med. 2021;18:2005–11.
9. Zarotsky V, Huang MY, Carman W, Morgentaler A, Singhal PK, Coffin D, et al. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. Andrology. 2014;2:819–34.
10. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281:537–44.
11. Genchi VA, Rossi E, Lauriola C, D'Oria R, Palma G, Borrelli A, et al. Adipose tissue dysfunction and obesity-related male hypogonadism. Int J Mol Sci. 2022;23:8194.
12. Sairam K, Kulinskaya E, Boustead GB, Hanbury DC, Mcnicholas TA. Prevalence of undiagnosed diabetes mellitus in male erectile dysfunction. BJU Int. 2001;88:68–71.
13. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307:491–7.
14. Molina-Vega M, Asenjo-Plaza M, Banderas-Donaire MJ, Hernández-Ollero MD, Rodríguez-Moreno S, Álvarez-Millán JJ, et al. Prevalence of and risk factors for erectile dysfunction in young nondiabetic obese men: results from a regional study. Asian J Androl. 2020;22:372–8.
15. Andersen I, Heitmann BL, Wagner G. Obesity and sexual dysfunction in younger Danish men. J Sex Med. 2008;5:2053–60.
16. Han TS, Tajar A, O'Neill TW, Jiang M, Bartfai G, Boonen S, et al. Impaired quality of life and sexual function in overweight and obese men: the European Male Ageing Study. Eur J Endocrinol. 2011;164:1003–11.
17. Janiszewski PM, Janssen I, Ross R. Abdominal obesity and physical inactivity are associated with erectile dysfunction independent of body mass index. J Sex Med. 2009;6:1990–8.
18. Di Vincenzo A, Busetto L, Vettor R, Rossato M. Obesity, male reproductive function and bariatric surgery. Front Endocrinol (Lausanne). 2018;9:769.
19. Sarwer DB, Spitzer JC, Wadden TA, Rosen RC, Mitchell JE, Lancaster K, et al. Sexual functioning and sex hormones in persons with extreme obesity and seeking surgical and nonsurgical weight loss. Surg Obes Relat Dis. 2013;9:997–1007.
20. Wake DJ, Strand M, Rask E, Westerbacka J, Livingstone DEW, Soderberg S, et al. Intra-adipose sex steroid metabolism and body fat distribution in idiopathic human obesity. Clin Endocrinol (Oxf). 2007;66:440–6.
21. Jeibmann A, Zahedi S, Simoni M, Nieschlag E, Byrne MM. Glucagon-like peptide-1 reduces the pulsatile component of testosterone secretion in healthy males. Eur J Clin Invest. 2005;35:565–72.
22. Caltabiano R, Condorelli D, Panza S, Boitani C, Musso N, Ježek D, et al. Glucagon-like peptide-1 receptor is expressed in human and rodent testis. Andrology. 2020;8:1935–45.
23. Li S, Lu MM, Zhou D, Hammes SR, Morrisey EE. GLP-1: a novel zinc finger protein required in somatic cells of the gonad for germ cell development. Dev Biol. 2007;301:106–16.
24. Grau-Bové C, González-Quilen C, Cantini G, Nardini P, Espina B, Bani D, et al. GLP1 exerts paracrine activity in the intestinal lumen of human colon. Int J Mol Sci. 2022;23:3523.
25. Ferreira JP, Böhm M, Rossignol P, Zannad F. Impact of anti-hypertensive therapy in the sexual health of men and women: an analysis from the SPRINT trial. Am J Hypertens. 2021;34:760–72.
26. Henderson T, Shepheard J, Sundararajan V. Quality of diagnosis and procedure coding in ICD-10 administrative data. Med Care. 2006;44:1011–9.

AUTHOR CONTRIBUTIONS

Corey Able: Idea generation, data collection, data analysis, manuscript writing, manuscript editing. Brian Liao: Data collection, data analysis, manuscript writing. Gal Saffati: Manuscript writing, manuscript editing. Ankith Maramanda: Manuscript writing, manuscript editing. James Applewhite: Manuscript writing, manuscript editing. Ali A. Nasrallah: Idea generation, manuscript writing, manuscript editing. Joseph Sonstein: Idea refinement, manuscript editing. Laith Alzweri: Idea refinement, manuscript editing. Taylor Kohn: Idea refinement, data analysis, manuscript editing.

COMPETING INTERESTS

The authors declare no competing interests.

ATTESTATION STATEMENT

Data regarding any of the subjects in the study has not been previously published. Available data will be made available to the editors of the journal for review or query upon request.

ADDITIONAL INFORMATION

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