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RESEARCH ARTICLE

Abdulmajeed et al: Bariatric metabolic surgery and cancer risk

Bariatric metabolic surgery and cancer risk: Target trial emulation using iterative time distribution matching

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ABSTRACT

Bariatric metabolic surgery (BMS) is a common intervention for severe obesity, yet its effects on cancer risk remain unclear. Observational studies and meta-analyses yield inconsistent findings, while randomized controlled trials often lack adequate follow-up to evaluate cancer outcomes. This study aims to emulate a target trial using observational data, employing a transparent and robust methodology to address this issue. We constructed a large retrospective cohort of adults with obesity in Qatar using electronic medical records from the public health system, with data available from 2018. We developed and applied iterative time distribution matching (ITDM) which is an iterative version of prescription time distribution matching (PTDM) as an improved approach to mitigate immortal time bias. This adaptation facilitated the alignment of time-zero (T_0) between BMS recipients and non-recipients. Subsequently, we applied a Cox proportional hazards regression model, controlling for confounders and prognostic covariates, for data analysis. The final study cohort comprised 124,780 individuals aged 30 years and older, including 1,465 who underwent BMS and 1,583 who developed cancer during the follow-up period. The median follow-up duration was 7.79 years (IQR: 4.89–10.85). In the confounder- and prognostic covariate-adjusted Cox model, BMS was associated with a reduced hazard of cancer (HR 0.49, 95% CI 0.31 to 0.76). Given potential residual confounding and the limited outcome data, these findings provide preliminary evidence of a protective association and should be interpreted cautiously. This approach emphasizes transparency in trial emulation design, and future studies should focus on specific cancer types and long-term outcomes as additional data become available.

Keywords: Cancer, bariatric metabolic surgery, immortal time bias, iterative time distribution matching, observational study.

INTRODUCTION

Obesity is a well-established risk factor for developing many chronic diseases, such as type 2 diabetes, cardiovascular disease, and cancer[1–3]. Several biological mechanisms linking obesity to cancer initiation and progression have been delineated[3,4], and it has been estimated that approximately 3.6% of all newly diagnosed cancers worldwide and 13% of obesity-related cancers in adults aged 30 years or more could presumably be linked to an increased BMI[5,6]. Bariatric metabolic surgery (BMS) is increasingly being used to mitigate the consequences of obesity, and long-term evidence on the efficacy and safety of BMS has continued to accrue over the past 25 years. Yet, its impact on cancer risk remains unresolved. A multitude of observational studies have investigated the association of BMS for severe obesity with the risk of cancer. However, results remain conflicting, with some studies reporting that patients undergoing BMS had a significantly reduced risk of developing cancer[7,8], and others either do not concur or do not find a reduction in risk for men, for the elderly, or for certain cancers, especially upper gastrointestinal cancers[9–17]. Meta-analysis of such observational data has also been conflicting[18,19]. In the past 15 years, at least 13 RCTs have compared BMS with lifestyle and medical therapy for the treatment of type 2 diabetes, showing that BMS results in significantly larger short to mid-term improvements in glycemic control, disease remission, cardiovascular risk factors, and chronic kidney disease[20]. These RCTs have been unable to examine cancer risk because of their limitations, including small sample sizes and inadequate duration to detect differences in several important outcomes, including cancer and cardiovascular disease. In addition, the type of non-surgical treatments (lifestyle, drugs, exercise) and adherence to the program varied between studies.

Given the ongoing uncertainty, one solution is to strengthen the observational design to make it more reliable in terms of causality by emulating a target trial's synchronization of eligibility and assignment at time-zero (T_0). This approach is particularly feasible and valuable given the availability of large databases. A single attempt to do so was made in 2022[21] but the emulation of the target trial did not seem to achieve synchronization of assignment (to BMS or not) with eligibility at T_0 of follow-up (see discussion). To optimize this design, the target trial to be emulated would need to estimate the joint effect of the operative and postoperative components

[22] by randomly assigning individuals to either (1) successfully complete the preoperative period and undergo BMS and postoperative monitoring or (2) no surgery during the follow-up. Against this background, the objective of the present study was, therefore, to investigate the association between BMS and the incidence of any cancer in adults within the context of an appropriately emulated target trial where eligibility and assignment to the intervention could be considered synchronized at T_0 given the methods used .

MATERIALS AND METHODS

Study design and setting

This study was designed to emulate a target trial using observational data to estimate the causal effect of BMS on cancer risk. We used patient data obtained from the Business and Health Intelligence (BHI) department at the Primary Health Care Corporation (PHCC) in Qatar. The electronic medical record system (Cerner Millennium) was established in 2016 and was fully operational by 2018. This is a shared platform among all public health providers, including secondary and tertiary care centers such as Hamad Medical Corporation (HMC) and the National Center for Cancer Care and Research (NCCR).

Study population and variables

Adults who had an encounter with the system between 2018 to 2024 were eligible if they had at least one obesity-related BMI measure (≥30 kg/m^2) before age 40, as we could not determine a more specific date for the obesity diagnosis. We used BMI even though BMI is an imperfect surrogate for adiposity and cancer-relevant biology (it does not capture fat distribution or body composition and may misclassify risk across age and ethnic groups). Nevertheless, we are of the opinion, as has been suggested in a recent paper [23], that BMI can be used in the screening of patients with potential obesity. Key variables included demographics (age, gender, nationality), clinical diagnoses (cancer and other obesity-related complications), anthropometric measures (BMI records), BMS details, and relevant dates (birth, diagnoses, BMS, last healthcare encounter, and death). Next, we assigned the following dates: The date at which participants reached age 30 as the date of origin, the date of BMS for those who underwent such surgery, and the date of exit defined as the date of cancer diagnosis, date of death, last recorded healthcare encounter, or December 31, 2024,

whichever occurred first. We then excluded individuals following a stepwise approach, as follows:

Individuals with cancer diagnoses prior to age of 30 were excluded.

Individuals with the date of exit before age of 30 were excluded.

Individuals who underwent BMS prior to age 30 were excluded.

Individuals who received BMS after diagnosis of cancer were excluded.

We now had a cohort of patients with no cancer and who did not undergo BMS till age 30 years, but who may have undergone BMS after age 30.

Emulating a target trial

The causal question was whether BMS reduces incident cancer diagnosis over follow-up. A pragmatic trial would synchronize the initiation of the two treatment strategies (BMS or not) with eligibility criteria (adults with obesity but without cancer at age 30y) at T_0 of follow-up. Such synchronization of eligibility and treatment assignment at T_0 is a key principle of study design that arises naturally in randomized trials (*Supplementary Table S1, emulation protocol*).

To emulate this target trial with observational data and therefore mitigate immortal time, lead time, and survivor bias, we needed to avoid misclassifying follow-up time. This was necessary because individuals could meet the eligibility criteria continuously after age 30y and therefore multiple times qualify as T_0 for both those receiving BMS or not[24]. There have been several options described in the literature to ensure that follow-up time is not misclassified, including prescription time distribution matching (PTDM), sequential Cox models, time-dependent Cox models, and the marginal structural Cox model[25]. We found PTDM to be a straightforward and transparent approach that utilizes fewer analytical assumptions to deal with the problem of immortal time bias. However, there have been reports of residual bias, with PTDM because it assigns T_0 in a single iteration, following which it may also end up being assigned after the end of follow-up to some individuals who are then excluded from the analysis, making the final time distribution (in analysis) less comparable across groups. To correct this, we distributed immortal time in the surgery group (time from date of age 30y to date of BMS) randomly (with replacement) to the BMS non-recipients over several iterations.

Similar to PTDM[26,27], the process starts with setting the time of treatment initiation (which is also the end of the immortal time period) as T_0 in the BMS-recipients. Next, the immortal time for all BMS-recipients (from date of age 30y till T_0) is listed, and one of the latter is randomly assigned (with replacement) as the immortal time for each of the BMS non-recipients, thereby assigning them a T_0. This whole process is iterated multiple times so that there are multiple columns for T_0, resulting in a row vector of possible T_0 created for each BMS non-recipient. Ineligible row values (beyond the date of exit from the study) are set to missing and the maximum across the first, first two, first three, and so on are selected as possible T_0 such that we have a sequence of maximum T_0 values (mT_{01},mT_{02},mT_{03}...,mT_{0k}) , based on the number of iterations for each BMS non-recipient. The final mT_0 used as T_0 for BMS non-recipients was that belonging to the number of iterations, *k*, where the overall Kolmogorov–Smirnov *D* value was minimum. This was visualized using a transition plot which is a plot of the overall Kolmogorov–Smirnov *D* value comparing the distribution between groups against iteration number (see *supplementary Figure S1*). This was further confirmed using cumulative distribution plots (distplot in Stata; see *supplementary Figure S2*). We named this new method the Iterative Time Distribution Matching (ITDM) method, which follows the same process as PTDM except that now there was a possibility that the time distribution will actually be aligned before analysis and drop-outs due to invalid assignment of T_0 is minimized.

Confounder selection

A directed acyclic graph (DAG) was developed using dagitty.net to inform the selection of a minimal adjustment set. Qatari nationality, gender, type 2 diabetes at origin, Class III obesity (BMI ≥ 40 kg/m² or not) at origin, age at entry to risk[28] and smoking status were prognostic factors for cancer[29] as well as associated with selection for BMS (Supplementary Figure S3) and formed the minimum adjustment set. It was assumed that any selection bias that might have been caused by informative censoring would be mitigated by adjusting for the covariates that influence selection into the intervention groups (Supplementary Figure S3). Achieving weight loss trajectory and metabolic remission were considered mediators of the BMS-cancer effect in the DAG.

Ethical statement

This study was reviewed and approved by the Institutional Review Board (IRB) of the Primary Health Care Corporation, ref no.: BUHOOTH-D-24-00045. The Qatar University Institutional Review Board (QU-IRB) granted a review exemption, ref no.: QU-IRB 072/2025-EM. The study utilizes de-identified data from a population health repository, ensuring that participant confidentiality and privacy are maintained in accordance with ethical guidelines and institutional policies. Informed consent was not required as the study involves secondary data analysis without direct participant interaction.

Statistical analysis

Since the ITDM algorithm is inherently iterative, the final inclusion set can vary slightly across computers even when same seed values are used. Therefore, we performed iterations with multiple seed values (see code in supplementary material) until maximal participant numbers with failures were observed to be included and then saved that dataset for the final analysis. The original and ITDM cohorts were compared descriptively. A descriptive survival analysis of the BMS non-recipient cohort (after exclusions of those with cancer prior to age 30y) was undertaken to determine cancer incidence (per 1000py) and cumulative survival in those who did not undergo BMS. These estimates were provided over age-bands (0-5, 5-10, 10-15 and 15+ years following age 30y) for cancer incidence and at 5, 10 and 15 years from age 30y for cumulative cancer-free survival.

A stratified Cox proportional hazards regression analysis was conducted on the ITDM cohort, stratified by gender and smoking status and adjusted for age at entry [28] and other covariates determined through the DAG. An *important* point to note is that we needed to run the 10-iteration sequence once only to create the ITDM cohort for analysis because we had a relatively large dataset. With smaller datasets, this sequence of 10-iterations will need to be run multiple times till the best transition plot is realized given the fact that alignment is much more variable (per run) in such datasets. The results of the stratified Cox model estimated the causal association between BMS and cancer risk, reporting the results as hazard ratios (HRs). Time of origin within the Cox model was set at date of age 30y, to make age the time-scale, with entry to risk set at T_0. This was a per protocol analysis, performed by censoring at the last recorded encounter on the system. It provides a valid estimate when the

censoring is non-informative [30]. The DAG suggests that the adjustment for prognostic covariates by simple multivariable regression will mitigate selection bias due to dependent censoring [31]. The relative effect from the Cox model was also translated to a measure of impact by combining the hazard ratio with cancer-free survival obtained from the earlier analysis of the BMS non-recipient cohort. We further compared the naïve (ignoring immortal time), PTDM, and ITDM methods to assess differences in time alignment and their impact on the estimated association between BMS and cancer risk

To determine if the study data were consistent with a population model that assumes no effect (tested hypothesis), a *p* value was computed. The exact *p* value was reported and indicates the degree of significance of the estimated effect given the tested hypothesis, had it been the source of the study data. Results in the interval $p<0.05$ were labeled 'statistically significant' under the tested hypothesis[32]. To assess clinical benefit, the point estimate and its 95% confidence interval (CI) were reported, indicating the range of test hypotheses under which the study data would fall within the central 95% of the distribution specified in these models [32]. All analyses were conducted using Stata (version 18; Stata Corp, College Station, TX).

RESULTS

Cohort characteristics

As shown in Figure 1, we identified a total of 163,447 adults with more than one documented BMI ≥30 before age 40. Of this initial cohort, 2,349 had undergone BMS and 2,112 had a recorded cancer diagnosis. Surgery recipients in our dataset included 81.7% (n = 1,921) sleeve gastrectomy procedure, while Roux-en-Y Gastric Bypass accounted for 18.2% (n = 428). Cancer cases included various malignancies coded using ICD-10AM nomenclature, with the most common being thyroid cancer (C73, n=461), breast cancer (C50, n=392), and colorectal cancer (C18, n=60). The full distribution of cancer types is provided in *Supplementary Table S2.*

The incidence of cancer in those without BMS varied across follow-up time, from age 30y. In the first five years, the incidence rate was 0.96 (95% CI: 0.89–1.05) per 1,000 person-years, increasing to 2.58 (95% CI: 2.41–2.77) in the next 5 years. The rate further rose to 3.13 (95% CI: 2.80–3.50) in the subsequent 5 years and peaked at 6.75

(95% CI: 4.52-10.07) beyond 15 years of follow-up. Kaplan-Meier survival estimates showed a corresponding decline in cancer-free survival probability, from 99.5% (95% CI: 99.46-99.55%) at 5 years to 98.2% (95% CI: 98.08-98.28%) at 10 years and 96.4% (95% CI: 96.15-96.66%) at 15 years. Table 1 reports the gender-specific rates.

To define eligibility at age 30y, exclusions were applied in sequence. Individuals diagnosed with cancer before the study date of origin were excluded (n=362), along with those whose follow-up ended before the study's date of origin (n=24,585). Participants who underwent BMS before age 30 were excluded (n=475 and those undergoing BMS after diagnosis of cancer (n=11) were also excluded. After these exclusions, the refined cohort consisted of 138,014 individuals available for analysis, including 1,465 individuals who underwent BMS and 1,737 diagnosed with cancer.

Assignment of T_0

As per the analysis plan, we followed the ITDM approach to perform T_0 assignment in non-recipients of BMS (unexposed). Optimal iteration selection was based on two complementary approaches: (1) quantitative assessment of immortal-time distribution alignment across the two comparison groups using the Kolmogorov–Smirnov D statistic, a measure of distributional difference, which remains independent of sample size and (2) visual inspection of the corresponding distribution plots. In this analysis, iteration 6 had the lowest D value and also demonstrated the best overlap between groups in the distribution plots. The ITDM Transition Plot and the distribution plots from the multiple iterations are provided as supplementary material (*supplementary Figures S1, S2*). There were still 13,234 BMS non-recipients who now had T_0 after exit from the risk set, and these dropped out of the analysis. The entire process above led to the removal of 529 cancer cases including 148 blood cancers, 128 thyroid cancers, 60 breast cancers, 43 reproductive system cancers, 28 gastrointestinal cancers, and 122 cases of other malignancies. These exclusions were necessary to maintain the alignment of follow-up time. The detailed breakdown of the excluded cancer cases is provided in *Supplementary Table S2*. The final analysis included 124,780 individuals, with 1,583 failures (down from 1,737 that we started with) in a single-failure-per-subject dataset.

Description of the analysis cohort

The final analysis cohort included 124,780 individuals, of whom 1,465 (1.17%) were BMS recipients. The median age at entry (age at T_0) was 35.87 years (IQR: 33.25-38.63). Women accounted for 61.17% (n=76,331) of the cohort and 69.90% (n=1,024) of BMS recipients. Qataris constituted 20.67% (n=25,795) of the overall cohort but represented 86.08% (n=1,261) of BMS recipients. class III obesity (BMI ≥ 40 kg/m²) at baseline was present in 11.13% (n=13,893) overall and markedly higher among BMS recipients (56.93%, n=834). Median follow-up was 7.79 years (IQR: 4.89–10.85). Cancer occurred in 1.27% (n=1,583) of individuals overall, with a slightly higher incidence among BMS recipients (1.43%, n=21). The latter is a naïve crude comparison given that immortal time is included. Detailed characteristics of the cohort are presented in Table 2.

Cox regression analysis

The stratified Cox regression analysis, after adjusting for confounders and prognostic covariates, suggested a statistically significant benefit of surgery (HR, 0.49; 95% CI, 0.31–0.76; p=0.002) which was also practically important. The E-value was 3.50 for the point estimate and 1.96 for the upper CI bound. The HR translated to numbers needed to treat (NNTs) of 409, 125, and 69 for males and 393, 98, and 48 for females at 5, 10, and 15 years of follow-up, respectively. Therefore, at 15 years of follow-up, there was one less cancer observed for every 69 surgically versus non-surgically managed males with obesity and 48 surgically versus non-surgically managed females with obesity (Table 1). Model diagnostics indicated adequate fit, with the global goodness-of-fit plot (*supplementary Figure S4*) showing close agreement between observed and expected cumulative hazard functions. To assess proportionality, a stratified proportional-hazards test (stphtest) was performed. Stratification by gender and smoking status yielded a global PH test (χ^2 = 7.15, p = 0.209), indicating acceptable proportionality. The log–log survival curves (Figure S5) showed broadly similar patterns for surgery status and other covariates across most of the follow-up period, with divergence only at the extremes, suggesting approximate compliance with the proportional-hazards assumption for the main exposure. Sensitivity analysis was performed to assess the influence of the limited number of cancer cases among surgery recipients (n=21). Repeating the analysis multiple times while randomly removing two BMS recipients with cancer had no material impact on the effect

estimates, indicating robustness to potential outcome misclassification (see *Supplementary Table S3*).

Comparison of three methods

Figure 2 shows how misalignment of immortal time affects the comparison between the two groups in survival analysis. The top panel in Figure 2 depicts how the survival curve alignment is dependent on the correct assignment of T_0. The naïve analysis ignores immortal time. The PTDM fully corrects the misalignment of T_0 but assigns a large number of T_0 beyond the participants' date of exit from the study. This resulted in a worse misalignment than even with the naïve method during analysis, due to exclusions (middle panel of Figure 2). With the ITDM, the misalignment, due to dropping participants, is largely avoided thereby preserving the failure pool (1,583 failures) but more importantly aligning immortal time correctly. This is depicted by the distribution plot in the right panel. There were 1737, 978, and 1583 failures observed in single-failure-per-subject data for the naïve, PTDM, and ITDM methods respectively, indicating that with ITDM not only was misalignment of immortal time minimized, exclusions were also markedly minimized. The dropped individuals with failures were all among BMS non-recipients.

DISCUSSION

Obesity is a chronic and life-threatening condition that has been strongly linked to an increased risk of certain cancers. Every year, approximately 5% of new cancer cases in men and 10% in women are attributable to excess body weight, underscoring the global burden of obesity-related malignancies[33]. Furthermore, the International Agency for Research on Cancer (IARC) has identified 13 cancers for which there is sufficient evidence to conclude that excess adiposity is a causal factor, including common malignancies such as colorectal, thyroid, and postmenopausal breast cancer[34]. The mechanisms behind this relationship are multifaceted and likely cancer-specific, with chronic inflammation, dysregulated immunity, hyperinsulinemia, and alterations in sex hormone metabolism all playing potential roles[2,35]. In this context, our study provides new evidence for the effect of BMS on subsequent cancer development. We observed a lower risk of cancer among individuals who underwent BMS, with a hazard ratio (HR) of 0.49 (95% CI, 0.31, 0.76) in our synchronized, confounder and prognostic covariate-adjusted Cox proportional hazards model. These

results suggest that there is a statistically significant (p=0.002) estimated effect, with a point estimate that demonstrates strong benefit for those who undergo BMS in terms of cancer risk.

Among surgical procedures, Roux-en-Y gastric bypass has been reported to provide greater benefit compared to laparoscopic sleeve gastrectomy[36], but similar comparisons were not possible in our analysis due to the limited number of cancer cases after BMS. This observation could possibly reflect the degree of weight loss associated with each procedure. Despite the overall benefit of BMS, there has been a suggestion that one type of BMS (gastric bypass) is associated with a higher risk of colorectal cancer[11,13,37]. In contrast, other studies have observed a potential reduction in colorectal cancer incidence[8,38], or a non-significant effect estimate either favoring benefit[21,39] or indicating harm[40]. In this study, given the paucity of incident cancers in BMS recipients, we were unable to test this hypothesis within the modeling approach used. However, of the 41 cancers noted in BMS recipients, only 2 (5%) were gastrointestinal compared to 139 of 2071 cancers noted in BMS non-recipients (7%), suggesting no practical difference descriptively. Within our dataset, 65% of gastrointestinal cancers (92/141) were colorectal cancers. Concerns have also been raised about a potential link between sleeve gastrectomy and esophageal cancer due to its effects on gastroesophageal reflux disease (GERD) and Barrett's esophagus[41]. Recent studies have found a lower incidence of Barrett's esophagus following sleeve gastrectomy and no significant difference in reflux esophagitis rates between sleeve gastrectomy and gastric bypass[42]. Our dataset included only one case of esophageal cancer, making direct comparisons infeasible.

A key concern in observational studies of this type is immortal time bias. Immortal time bias occurs when follow-up time for certain groups is misclassified, typically by excluding periods during which events cannot occur. This is typically seen in cohort comparisons of exposed and unexposed individuals. If the distribution of the time between age 30y and T_0 is distributed differently in BMS recipients and non-recipients, it would artificially bias risk and the direction depends on the nature of the misalignment of follow-up time as is clearly depicted in Figure 2. The varying misalignment of follow-up time across groups in existing observational studies would explain their varying results when they have examined the incidence of all (or any) cancers following BMS[8,9,21,39,40,43–45]. The first panel in Figure 2 depicts what

most of these observational studies have done, and returns an adjusted HR of 0.70 (95% CI 0.45,1.09), which is in the range reported by existing studies and biased toward the null. While most of these studies did not explicitly address immortal time bias in the design or analysis of the study[46], one study by Lazzati et al. attempted to do so[21]. The authors report that they followed all subjects from the first diagnosis of obesity until cancer diagnosis, death, or censoring. However, the assignment to BMS occurred after the follow-up started and therefore there must still have been misclassification of follow-up time in their study, potentially introducing bias. In this study, we ensured that misclassification of follow-up time was explicitly addressed.

One of the major strengths of ITDM is its transparent strategy for mitigation of immortal time bias. This approach, unlike others, uses time alignment that does not change the target population much and the estimator does not rely on any unrealistic functional form assumptions[47]. The iterative process further strengthens this approach by systematically refining T_0 assignment in the non-surgery group until the distribution of immortal time aligns optimally with that of the surgery group. This ensures that lead time and survival advantages are not artificially introduced, improving the internal validity of the study. The extent of the distortion of the magnitude of measured associations reported by studies that continue to misclassify pre-exposure person time is dependent on three factors[48]: a) the mean pre-exposure (immortal) time b) the proportion of exposed individuals and c) the length of follow-up on study. The bias increases as the immortal time and proportion of exposed participants in the study population increases and decreases as length of follow-up increases. The impact of the first factor (immortal time) seen in this study is vividly illustrated in Figure 2.

Despite the strengths of our approach, several limitations should be acknowledged. First, this remains an observational study, and even methodologies such as ITDM cannot eliminate all potential biases. Second, target trial emulation resolves problems related to incorrect design but not those related to data limitations [49]. Despite our best efforts to obtain accurate data, our data sources may have encountered some errors in BMI measurement, dates, or cancer diagnoses, given their dependence on data entry systems on the electronic medical record. For example, smoking status was incompletely measured, with over half the cohort with no information on their smoking status, limiting the effectiveness of adjustment. Third, though our DAG

depicts the minimal adjustment set that may mitigate bias due to dependent censoring, all such variables may not have been captured leading to residual bias. A major variable, nationality, was accurately recorded and included in the adjustment set, which should largely mitigate bias from this source (see the DAG in *supplementary Figure S3*), however, because the DAG does not include variables we did not capture, residual and unmeasured confounding remain possible. Fourth, the relatively shorter follow-up for some participants, and the sparseness of cancer outcomes after BMS should be considered in the interpretation of these results as they limited procedure-specific analyses. Most of our BMS non-recipients were residents who had a shorter follow-up than citizens. Fifth, data on post-operative weight loss, BMI change, or metabolic remission were not available in our dataset. However, these variables are likely mediators of the effect of BMS on cancer risk and their absence is unlikely to materially affect the direction and magnitude of our estimate (see DAG in *supplementary material Figure S3*). Nevertheless, it should be noted that these are our modelling assumptions based on the DAG that we have made explicit and other researchers may entertain other modelling assumptions that they are comfortable with. Cancer risk reduction after BMS is thought to arise from weight loss, hormonal changes, or both, with recent evidence pointing to a predominant hormonal effect, making our estimates likely conservative, if these targets were not met in some participants.

A strength of this paper is that we assessed risk for all cancers combined which can provide a more comprehensive estimate of the total disease burden associated with an exposure. Pooling all cancer types increases the number of cases, thereby improving statistical power and reducing random variation, while also avoiding the multiple comparisons problem inherent in analyzing many specific cancer types separately. This approach can reveal a net increase in cancer risk that might be missed when individual cancers show only modest or inconsistent associations, and it can serve as an early indicator of potential carcinogenicity for further site-specific investigation. However, all-cancer analyses may mask divergent site-specific effects, where an exposure increases risk for some cancers but decreases risk for others, so they should be complemented with future type-specific analyses to provide a complete risk profile.

CONCLUSION

This study provides preliminary evidence that BMS is associated with a lower hazard of cancer in a national EHR cohort using a target-trial emulation with ITDM. Because post-operative outcomes were unavailable and residual confounding is possible, the association should be interpreted cautiously. Larger datasets with procedure-specific outcomes and richer covariate capture are needed to refine effect estimates and explore site-specific risks. By integrating the emulation of a target trial approach, we strengthened our ability to draw much more credible, inferences from observational data. Future examination of the ITDM approach by others will ensure that target trial emulation methods continue to advance, and the simplicity of the approach may help increase the impact on epidemiologic research thus enabling real-world evidence to shape clinical decision-making with greater confidence.

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Data availability: The dataset generated and analyzed during this study is available from the corresponding author upon reasonable request.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Cancer incidence and cancer free survival without BMS and impact of BMS

Period in years from age 30y	Cancers	Person-years (per 1000)	Cancer incidence (per 1000 person-years)	Cancer free survival	NNT*
Males					
0-5	215	227.5	0.94 (0.83, 1.08)	At 5y: 99.5%	409
5-10	294	137.1	2.14 (1.91, 2.40)	At 10y: 98.4%	125
10-15	100	42.2	2.37 (1.95, 2.89)	At 15y: 97.1%	69
15+	5	1.5	3.43 (1.43, 8.25)		
Females					
0-5	340	348.8	0.97 (0.87, 1.08)	At 5y: 99.5%	393
5-10	541	186.0	2.90 (2.67, 3.17)	At 10y: 98%	98
10-15	202	54.5	3.71 (3.23, 4.26)	At 15y: 96%	48
15+	19	2.1	9.05 (5.77, 14.18)		
Final Cox PH model results**					
Hazard ratio	95% CI	z	$p>\|z\|$		
0.49	0.31, 0.76	-3.16	0.002		

*Based on a HR of 0.49; NNT, number needed to treat to prevent one additional case of cancer, is assessed over follow-up periods of 5, 10, and 15 years. **Adjusted for gender, Qatari nationality, type 2 diabetes at baseline, class III obesity (BMI ≥ 40 kg/m² or not) at origin, age at study entry, and smoking status. Abbreviations: BMS: Bariatric metabolic surgery; NNT: Number needed to treat; HR: Hazard ratio; PH: Proportional hazards; CI: Confidence interval.

Table 2. Characteristics of individuals included in the final analysis dataset.

	BMS recipients (*n*=1,465)	BMS non-recipients (*n*=123,315)	SMD	Overall (*n*=124,780)
Demographics				
Age at entry (T_0), years (median, IQR)	35.63 (32.74-38.72)	35.88 (33.25-38.63)	0.004	35.87 (33.25-38.63)
Female (*n*, %)	1,024 (69.90%)	75,307 (61.07%)	0.187	76,331 (61.17%)
Qatari (*n*, %)	1,261 (86.08%)	24,534 (19.9%)	1.771	25,795 (20.67%)
Obesity-related comorbidities at baseline				
Class III Obesity - BMI ≥ 40 kg/m² (*n*, %)	834 (56.93%)	13,059 (10.57%)	1.124	13,893 (11.13%)
Type 2 Diabetes (*n*, %)	40 (2.73%)	1,642 (1.33%)	0.099	1,682 (1.35%)
Hypertension (*n*, %)	30 (2.05%)	1,072 (0.87%)	0.098	1,102 (0.88%)
Dyslipidemia (*n*, %)	22 (1.50%)	1,102 (0.89%)	0.056	1,124 (0.90%)
Smoking Status				
Current smoker (*n*, %)	172 (11.74%)	10,004 (8.11%)	0.068	10,176 (8.16%)
Non-smoker (*n*, %)	633 (43.21%)	49,141 (39.85%)	0.122	49,774 (39.89%)
Missing/Unknown (*n*, %)	660 (45.05%)	64,170 (52.04%)	-0.140	64,830 (51.96%)
Follow-up, years (median, IQR)	10.09 (6.69-12.90)	7.77 (4.88-10.82)	0.461	7.79 (4.89-10.85)

Cancer cases (*n*, %)	21 (1.43%)	1,562 (1.27%)	0.014	1,583 (1.27%)

Abbreviations: BMS: Bariatric metabolic surgery; SMD: Standardized mean difference; IQR: Interquartile range; BMI: Body mass index.

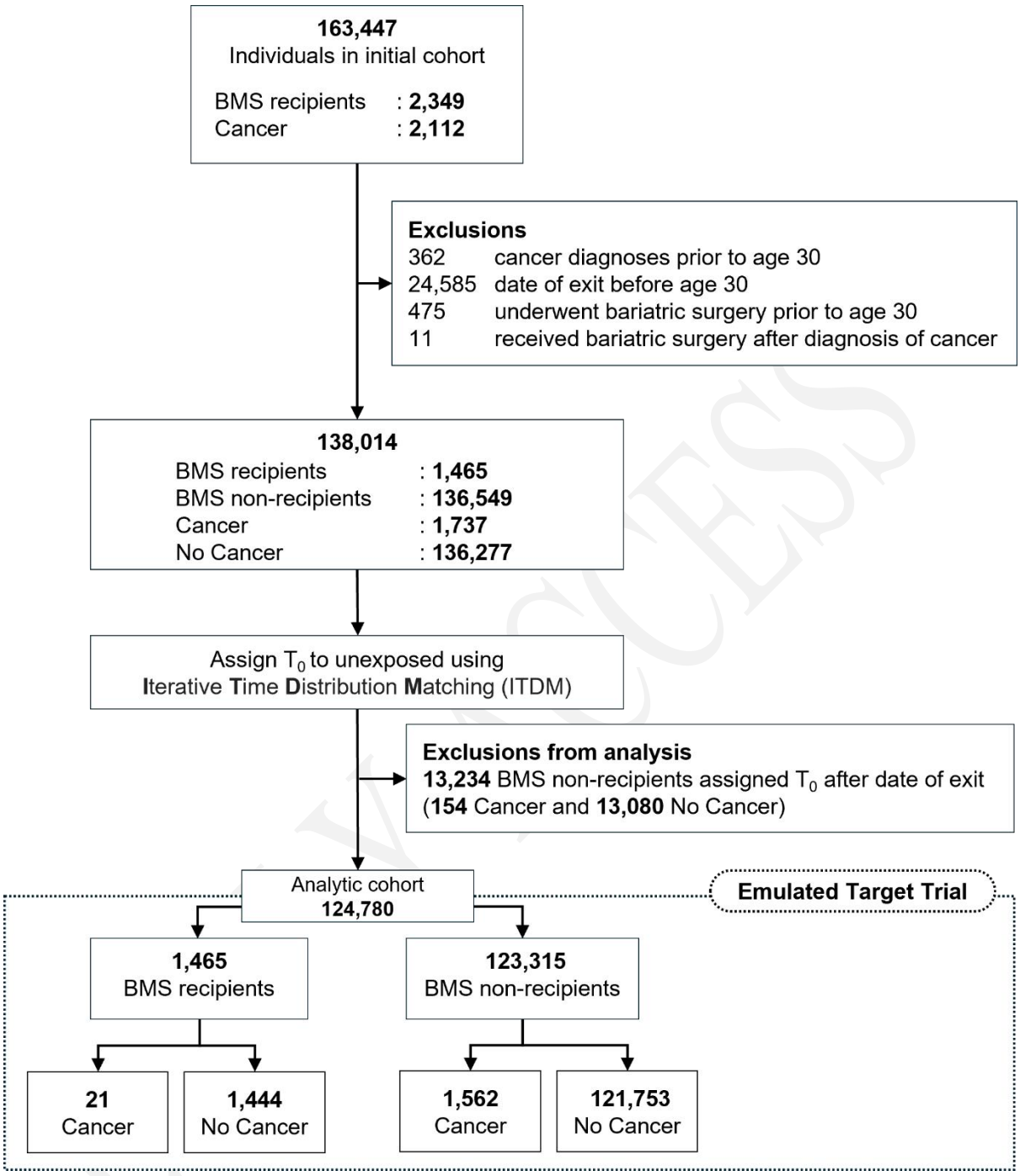

Figure 1. Cohort selection and emulation of target trial

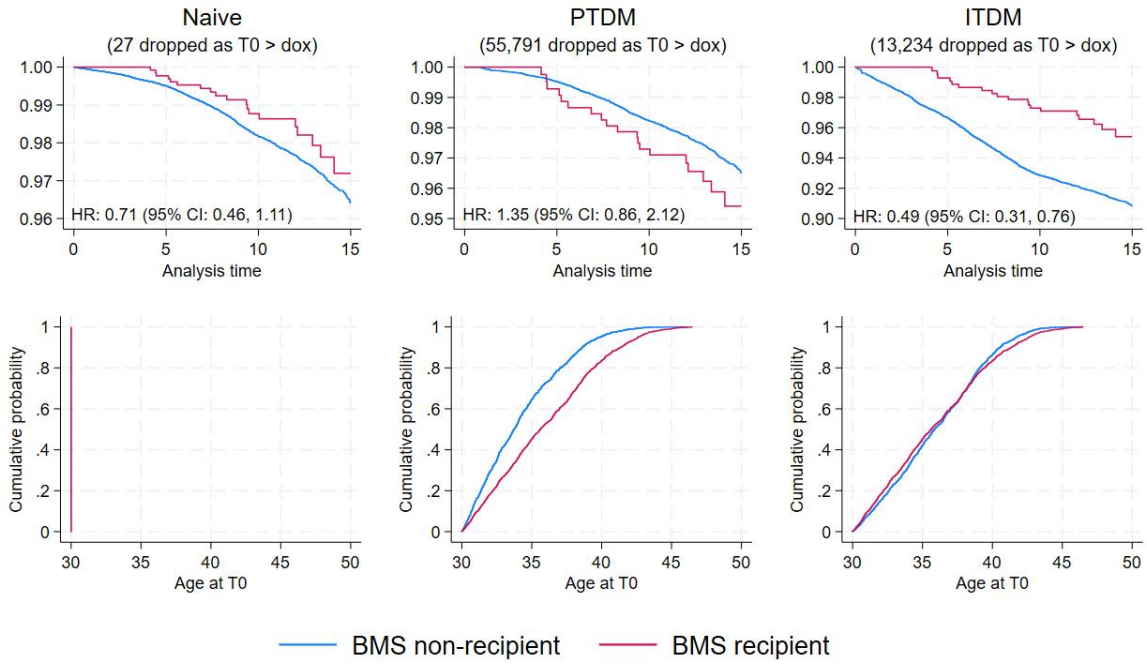

Figure 2. Comparison of three analytical approaches. The top row illustrates unadjusted survival curves, while the bottom row displays the distribution of assigned immortal time across groups (with no immortal time assigned in the left-most panels). The left panel shows 1,737 failures, the middle panel shows 978 failures, and the right panel shows 1,583 failures observed in single-failure-per-subject data. All individuals who were excluded (failures) were members of the BMS non-recipient group. Abbreviations: BMS: Bariatric metabolic surgery; PTDM: Prescription time distribution matching; ITDM: Iterative time distribution matching; HR: Hazard ratio; CI: Confidence interval; dox: Date of exit from the study.

SUPPLEMENTAL DATA

Supplemental data are available at the following link:

https://www.bjbms.org/ojs/index.php/bjbms/article/view/12842/4040