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Gallbladder disease in transgender individuals: associations with gender-affirming hormone therapy

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ABSTRACT

Background: Transgender individuals frequently undergo gender-affirming hormone therapy (GAHT) during their gender transition which plays a vital role in gender identity affirmation. Cholelithiasis, a common condition affecting 10-15% of the US population, has been linked to estrogen therapy in cisgender women. Despite the fact that hormonal profiles achieved after GAHT are not always identical to cisgender individuals, the effects of GAHT on gallbladder disease (GBD) risk have not been evaluated in transgender populations. This research aims to address this gap utilizing a large nationwide database.

Methods: The study analyzed medical records data from the TrinetX database from 52,847 trans men and 38,114 trans women. Four cohorts were created: trans women and men either receiving either hormone therapy or no intervention. Descriptive statistics were calculated before matching to estimate disease burden. The groups were then propensity score matched on known risk factors (age, race, BMI, etc.) and rates of GBD were compared.

Results: Before matching, trans women on hormone therapy (TWHT) had a significantly higher 10-year GBD probability than those naïve to therapy (TWNI) (4.69% vs 1.88%). For trans men, there was no significant difference in 10-year rates between those on therapy (TMHT) and those not (TMNI) (3.15% vs 3.87%). Cholecystectomy rates were significantly higher for TWHT than TWNI (1.10% vs. 0.57%), but similar between TMHT and TMNI (0.95% vs. 1.10%). After accounting for risk factors, TWHT had increased GBD risk (HR 1.832), while TMHT showed no significant change.

Discussion: This study suggests a link between estrogen GAHT and increased GBD risk in transgender women. Notably, testosterone GAHT did not offer protection against GBD in transgender men, contrary to expectations. This study is, to our knowledge, the first to describe the burden of GBD in the transgender population and to investigate the effects of GAHT on GBD risk.

KEYWORDS
Cholecystitis; cholelithiasis; estrogen; GAHT; HRT; testosterone

Introduction

Cholelithiasis, also known as gallstones, occurs when solid concretions, usually of cholesterol or bilirubin, form within the gallbladder. In the United States approximately 10–15% of the adult population has gallstones (Everhart et al., 1999). However, only one-third of individuals with gallstones experience symptoms, which occur when a gallstone obstructs the flow of bile into the biliary tree (Ahmed et al., 2000). While the mortality of gallstones is low at 0.6%, obstruction of the biliary tree by gallstones can result in complications including cholecystitis, choledocholithiasis, and cholangitis (Lammert et al., 2016).

Several well-documented risk factors contribute to gallstone formation including sex, age, race/ethnicity, obesity, rapid weight loss, pregnancy, and estrogen therapy (ET)(Pak & Lindseth, 2016). Among other mechanisms, estrogen increases biliary cholesterol secretion, which promotes the formation of cholesterol crystals and therefore gallstone formation (Uhler et al., 2000). Because of this, cisgender women are considered at higher risk of cholelithiasis than cisgender men due to their physiologically higher estrogen levels (Cirillo

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et al., 2005). The effect of hormone therapy on gallstone risk has not been explored in the context of gender-affirming therapy for transgender individuals.

In recent years, there is a growing recognition of transgender individuals, persons whose gender identity does not correspond with their sex assigned at birth (Meerwijk & Sevelius, 2017). Some transgender individuals choose to undergo gender-affirming interventions such as gender-affirming hormone therapy (GAHT) to align their body with their gender identity. Trans women (assigned male at birth) receive estrogen, often with an anti-androgen, while transgender men (assigned female at birth) are given testosterone. Gender affirming hormone therapy serves as a critical aspect of transgender healthcare and identity affirmation.

While the effect of ET on gallstone development has been extensively studied in cisgender women, with randomized control trials demonstrating an increased risk of gallbladder disease (Cirillo et al., 2005), there is a notable dearth of research exploring the effects of GAHT on gallstone development in trans women. Similarly, there has been no research into the effects of testosterone therapy on gallstone risk in transgender men. To our knowledge, there have been no studies that explored GAHT and gallstone disease in transgender populations.

The present study seeks to address this research gap by investigating the relationship between GAHT and gallbladder diseases in transgender patients. Through analysis of a large database, we aim to provide insights into gallstone-related complications in transgender patients undergoing GAHT, thereby contributing to a better understanding of the implications of hormone therapy in this specific population.

Materials and methods

Data source

We used US-based data from the network TriNetX (TriNetX, Inc., Cambridge, MA, United States), a multinational collaborative clinical research platform, that collects real-time medical records, including demographics, diagnoses, procedures, medications, laboratory values, and vital statuses. This network included 84 healthcare organizations at the time of analysis, including data from around 115.8 million patients. Sources of patient records were relatively evenly distributed across the United States (30% Northeast, 21% Midwest, 21% South and 27% West). The TriNetX platform uses aggregated counts and statistical summaries of de-identified information so that no protected health information or personal data are made available to users of the platform. Individuals with missing values for age at index were omitted from the data set. Data were extracted from the Research Network and analyzed on the TriNetX platform on June 23, 2023.

Study population

We queried the databank to select patients who identified as transgender based on the presence of ICD-10 codes indicating gender identity disorders (ICD-10 codes F64.0-F64.9). While chart review is the gold standard for identifying transgender patients in the medical record, studies demonstrate that ICD-10 based methods show a high specificity for identifying transgender patients in the EHR/EMR (Blosnich et al., 2018; Nik-Ahd et al., 2023; Proctor et al., 2016; Rich et al., 2021). We created 4 cohorts: trans women either receiving estrogen HT or no intervention (TWHT, TWNI) and trans men receiving testosterone therapy or no intervention (TMHT, TMNI). Estrogen and testosterone hormone therapy was defined using prescription codes and ICD-10 codes commonly used to denote GAHT (Appendix A). Patients were excluded from all groups who had a previous diagnosis of gallstone diseases or surgery affecting the biliary system before the index event. The index event for analysis was defined as 6 months past the earliest use of GAHT in the patient's medical record for the HT groups, or 6 months after the first GID diagnosis in the NI groups.

Outcomes

The primary outcome was the rate of gallbladder disease, determined by ICD-10 codes denoting

acute or chronic gallbladder inflammation or gallbladder or biliary tract stone disease (K80.0-8, K83.0-1,K81.0-9) (Cirillo et al., 2005). Secondary outcomes included rates of cholecystectomy, determined by CPT codes (Appendix A). The probability of each outcome was first evaluated in each cohort before matching using 1, 5, and 10 year Kaplan–Meier analysis in order to describe disease and surgical outcome burden. They were then compared between GAHT and non-GAHT groups post-matching to evaluate the potential effects of hormone therapy on gallstone disease risk.

Propensity score matching

Using 1:1 nearest neighbor propensity score matching (PSM) with a caliper of 0.1 times the pooled standard deviation of the propensity score, cohorts were matched on 27 gallstone disease-associated covariates including age, race, BMI, recent weight loss, alcohol and tobacco use, and presence of diabetes, HLD, and liver disease which were identified after comprehensive literature review. These covariates were identified using ICD-10 codes in the medical record prior to the index event. Following matching, standardized mean differences between the groups were < 0.035 for all covariates. Balance tables with full listed covariates are given (Appendix B).

Statistical analysis

The baseline characteristics for each group were compared with the chi-square test for categorical variables and the Student *t*-test for continuous variables. Before matching, Kaplan–Meier analysis was used to estimate the probability of gallbladder disease and surgical outcomes at 1 year, 5 years, and 10 years past the index event. Propensity score matching was then used to balance cohorts with baseline characteristics. In relation to outcome comparisons, we used the groups naïve to hormone therapy as the reference, comparing them with the hormone therapy groups. After matching, Kaplan–Meier analysis was performed to estimate the probability of outcomes after the index date from 1 day to the first instance of gallstones or the end of each patient's record (censoring date). Comparisons between cohorts were made using a log-rank test. We calculated hazard ratios (HRs) and their associated 95% confidence intervals (CI) via a Cox proportional hazards model, together with the test for proportionality based on the scaled Schoenfeld residual, using R's Survival package v3.2-3.

Statistical analyses were done within TriNetX. Statistical significance was set at a two-sided *p*-value of < 0.05.

Results

Baseline characteristics

We identified 52,847 trans men and 38,114 trans women. Within these groups, we identified 22,786 trans men using testosterone GAHT (TMHT), and 30,061 with no intervention (TMNI). There were 20,188 trans women on GAHT (TWHT) and 17,926 without (TWNI). The average time on treatment for individuals on GAHT was 853.4 d (SD 643.9, Range 1–7039) for trans men and 893.5 d (SD 810.7, Range 1–7353 d) for trans women.

The baseline characteristics of the cohorts are described in Table 1 and Appendix B. There were significant differences between TWHT and TWNI in rates of alcohol and nicotine dependence, as well as hyperlipidemia, cirrhosis, and NAFLD. Between TMHT and TMNI, there were significant differences in age at index, alcohol use disorder, Type 2 diabetes mellitus, hyperlipidemia, and NAFLD.

Outcomes

Before matching, the Kaplan–Meier showed that trans women receiving hormone therapy (TWHT) presented a significantly higher probability of all gallbladder disease outcomes at 1 year (0.38% vs 0.23%), 5 years (1.99% vs 1.08%), and 10 years (4.69% vs 1.88%), and cholelithiasis at 1 year (0.34% vs 0.21%), 5 years (1.83% vs 0.97%), and 10 years (4.26% vs 1.40%) compared to those without intervention (TWNI). For cholecystitis, the difference between TWHT and TWNI was significant only at the 1-year mark (0.10% vs 0.02%). For cholecystectomy, the rates were also significantly higher for TWHT at 1 year (0.11% vs 0.02%), 5 years (0.72% vs 0.34%), and 10 years (1.10% vs 0.57%).

Table 1. Baseline descriptive characteristics of transgender cohorts before propensity score matching.

	Transgender Women		Transgender Men	
Baseline characteristics	TWNI ($n=17926$)	TWHT ($n=20188$)	TMNI ($n=30061$)	TMHT ($n=22786$)
Age At Index, mean (SD), years	28.7 (14.7)	28.5 (13.0)	**25.4 (13.9)**	**24.5 (11.2)**
BMI, mean (SD)	26.4 (7.2)	26.2 (7.1)	26.4 (7.5)	27.5 (7.7)
Alcohol Consumption:				
Alcohol Use Disorder, Mild	317 (1.77%)	366 (1.81%)	**252 (0.84%)**	**250 (1.10%)**
Alcohol Use Disorder, Moderate-Severe	**219 (1.22%)**	**203 (1.01%)**	**149 (0.50%)**	**154 (0.68%)**
Nicotine Dependence	**952 (5.30%)**	**1510 (7.48%)**	**892 (2.97%)**	**1208 (5.30%)**
Type 1 Diabetes Mellitus	154 (0.86%)	202 (1.00%)	242 (0.81%)	210 (0.92%)
Type 2 Diabetes Mellitus	565 (3.15%)	664 (3.29%)	**685 (2.28%)**	**590 (2.59%)**
Hyperlipidemia	**1372 (7.64%)**	**2104 (10.42%)**	**1534 (5.10%)**	**1588 (6.97%)**
Fibrosis and Cirrhosis of the Liver	**68 (0.38%)**	**48 (0.24%)**	41 (0.14%)	38 (0.17%)
NAFLD	**144 (0.80%)**	**228 (1.13%)**	**179 (0.60%)**	**191 (0.84%)**
Alcoholic Liver Disease	30 (0.17%)	20 (0.10%)	17 (0.06%)	10 (0.04%)

TM: Trans Men; TW: Trans Women; HT: Hormone Therapy; NI: No Intervention. Bold indicates $p>.05$ between HT and NI groups within the same gender identity before matching.

Table 2. Kaplan–Meier Estimates of 1, 5, and 10 year probability of gallbladder disease and surgical outcomes before propensity score matching.

	% Patients with outcome											
	TWNI ($n=17,926$)			TWHT ($n=20,188$)			TMNI ($n=30,061$)			TMHT ($n=22,786$)		
Outcomes	1 year	5 year	10 year	1 year	5 year	10 year	1 year	5 year	10 year	1 year	5 year	10 year
All Gallbladder Disease	**0.23**	**1.08**	**1.88**	**0.38**	**1.99**	**4.69**	0.30	1.62	3.87	0.30	1.39	3.15
Outcomes:												
Cholelithiasis	**0.21**	**0.97**	**1.40**	**0.34**	**1.83**	**4.26**	0.26	1.46	3.57	0.28	1.22	2.93
Cholecystitis	**0.02**	0.29	0.92	**0.10**	0.44	0.56	0.09	0.42	0.78	0.07	0.38	0.79
Choledocholithiasis	0.03	0.07	0.17	0.02	0.13	0.40	0.03	0.08	0.08	0.01	0.10	0.10
Cholangitis	0.00	0.03	0.20	0.01	0.08	0.12	0.01	0.03	0.03	0.00	0.05	0.05
Surgical Outcomes:												
Cholecystectomy	**0.02**	**0.34**	**0.57**	**0.11**	**0.72**	**1.10**	0.07	0.42	1.10	0.09	0.41	0.95

TM: Trans Men; TW: Trans Women; HT: Hormone Therapy; NI: No Intervention. Bold indicates significant difference between HT and NI within same gender identity at same time point before matching (by K-M log-rank test, $p<.05$).

Table 3. Hazard ratio of gallbladder disease risk between propensity score matched cohorts.

	Cohort statistics		Log Rank Test		Hazard ratio	
Group	Patients in cohort	Patients with Gallstone Disease, No. (%)	X^2	p	HR	95% CI
TMHT	21,406	118 (0.55%)	1.547	.214	0.844	(0.645, 1.103)
TMNI	21,406	98 (0.46%)				
TWHT	15,900	123 (0.77%)	13.795	**<.0001**	**1.832**	(1.324, 2.533)
TWNI	15,900	52 (0.33%				

TM: Trans Men; TW: Trans Women; HT: Hormone Therapy; NI: No Intervention. Bold indicates statistical significance $p<.05$.

In contrast, trans men on hormone therapy (TMHT) displayed probabilities of 0.30% at 1 year, 1.62% at 5 years, and 3.87% at 10 years for all GBD outcomes, versus 0.30%, 1.39%, and 3.15% respectively for trans men not receiving hormone therapy (TMNI), with no significant differences observed at any time point. There was also no significant difference observed for cholecystectomy at any time point between TMHT and TMNI. The full pre-matching probabilities of gallbladder disease and surgery at 1, 5, and 10 years after the index event are given (Table 2).

Following propensity score matching, cohort sizes were 15,900 (for both TWHT and TWNI) and 21,406 (for both TMHT and TMNI) with standardized mean differences between groups of below 0.035 for all covariates.

After matching, we observed that trans women who received GAHT were more likely to be diagnosed with gallbladder disease than those who did not receive GAHT (Table 3). Cox proportional hazards models revealed an 83.2% (HR 1.832, 95%CI: 1.324, 2.533) increased hazard for TWHT vs TWNI. The log-rank test revealed a χ^2 of 13.795 with $p=.0002$ (Figure 1).

Among transgender men who received testosterone GAHT, we observed no significant difference in rates of gallbladder disease diagnoses. Cox proportional hazards models revealed an HR of 0.844 (0.95%CI: 0.645, 1.103) for TMHT

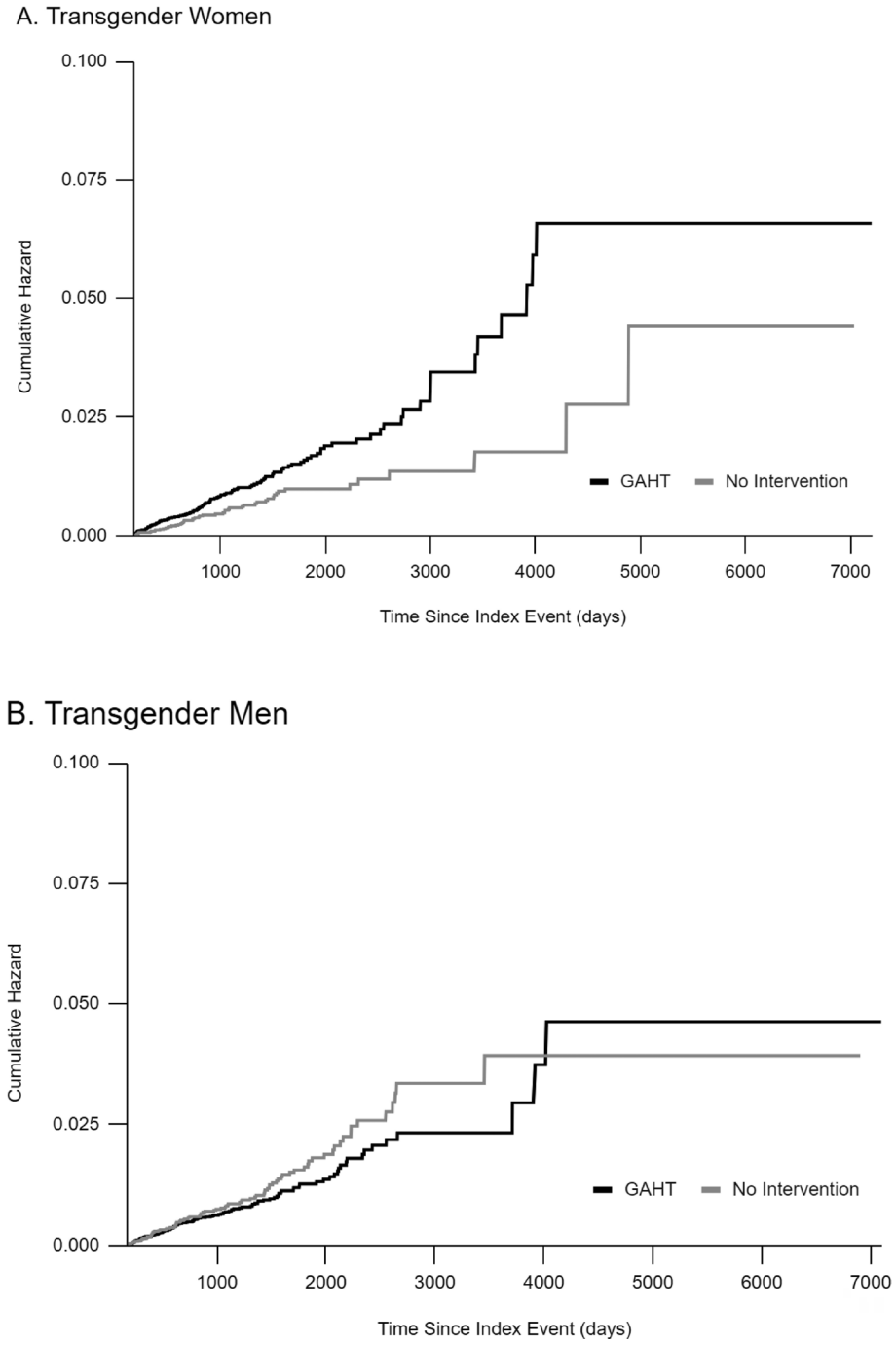

Figure 1. Kaplan–Meier estimates of cumulative hazards for gallbladder disease outcomes.

vs TMNI. The log-rank test revealed a χ^2 of 1.547 with $p = .214$ (Figure 1).

Discussion

In this study, we investigated the impact of Gender-Affirming Hormone Therapy (GAHT) on gallbladder disease rates in transgender patients. Cholelithiasis is common and leads to significant morbidity, mortality, and health care utilization in the United States and worldwide. Gallstones contribute to over 2.2 million ambulatory care visits and direct and indirect costs of over $6.5 billion annually (Unalp-Arida & Ruhl, 2022; Wadhwa et al., 2017). After adjusting for confounders, we found that transgender women on GAHT had a significantly higher likelihood of gallstone disease compared to those not on GAHT, while no such effect was seen in transgender men.

This is the first study to examine the relationship between hormone therapy and gallbladder disease in transgender individuals. To date, there have been two case reports published describing gallstone-related complications in transgender women (Freier et al. 2021, Tirthani et al. 2021). These case reports point to the administration of exogenous estrogen as a possible risk factor leading to the patients' biliary disease.

The gallstone promoting effects of estrogen hormone therapy may be attributed to the influence of estrogen in lipid metabolism. Estrogen increases the amount of cholesterol relative to bile salts and lecithin in bile, increasing the saturation of bile with cholesterol, which leads to cholesterol crystal formation. Estrogen also alters bile acid composition, increasing the chance of gallstone formation (Uhler et al. 2000).

Our results are consistent with prior studies showing that estrogen therapy (ET) elevates the risk of gallstones in cisgender individuals. In a randomized, doubled-blind, placebo-controlled trial, Cirillo et al. found that ET was associated with a significant excess risk of cholecystitis ((HR, 1.80; nominal 95% CI, 1.42–2.28; $p < .001$) and cholelithiasis (HR, 1.86; nominal 95% CI, 1.48–2.35; $p < .001$) in a sample of post-menopausal cis-gender women (Cirillo et al., 2005). Similarly, the HERS-II study found a 48% increased risk of biliary tract surgery in cis women receiving ET (Hulley et al., 2002).

We observed no significant change in gallstone disease burden in transgender men, contradicting our hypothesis that testosterone therapy would lead to lower estrogen levels and therefore lowered gallstone risk. There is limited research on testosterone hormone therapy's effects on gallbladder disease, although some studies suggest potential correlations between higher free testosterone levels and incident gallstone disease in cis males (Shabanzadeh, 2018; Squarza et al., 2018). One explanation could be that only about a third of trans men receiving GAHT experience a decrease in serum estradiol to cis male levels, indicating that testosterone GAHT alone may not be sufficient to decrease gallbladder disease risk in this group (Deutsch et al., 2015).

Our study's strengths include a notably large cohort size, which is particularly important given the typically small samples in transgender research. This large sample allows us to examine rare outcomes in this population such as cholangitis. The dataset's geographic and racial diversity adds to its representativeness. Moreover, our methodology effectively controls for various confounders, offering clearer insights into the relationship between GAHT and gallbladder disease in transgender people.

However, several limitations warrant acknowledgment. Propensity score matching may not entirely offset unmeasured or residual confounding. As with all studies using EMR data, the accuracy and completeness of the medical record is a potential source of error. Furthermore, healthcare access disparities among our population may contribute to underrepresentation of certain covariates and outcomes. An additional limitation is the possible sex assigned at birth misclassification in the TriNetX database. Though TriNetX offers a field denoting sex assigned at birth, it is possible that an individual's identified gender may have been reported instead. Since sex assigned at birth carries a higher weight biologically when it comes to medical decisions, we believe most EMR systems still register patients with their sex assigned at birth. Due to TriNetX platform limitations, we couldn't include a robust cisgender comparison group. As a result, our analysis is limited to comparing transgender groups with and without hormone therapy. Different criteria for follow-up between groups could introduce bias as different groups may have longer or shorter follow-up. The ICD-10 codes used offer high specificity but lower sensitivity, potentially omitting some members of the transgender population, though those identified are very likely to be transgender. (Blosnich et al., 2018; Nik-Ahd et al., 2023; Proctor et al., 2016; Rich et al., 2021).

Conclusion

Our study points to a link between estrogen hormone therapy and a heightened risk of gallbladder disease in transgender women. We also found that there is no significant decrease in gallstone risk for transgender men receiving GAHT. Our findings underline the importance of close monitoring for cholelithiasis and other gallbladder diseases in transgender patients receiving hormone therapy. Further research is needed to clarify best practices for early intervention and screening in this population. Our

study adds to the growing understanding of GAHT in the trans population, enhancing efforts to improve health and well-being among transgender individuals.

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Appendix A. Cohort and outcome criteria

Cohort Construction- Terms Denoting Gender Identity Disorders

	ICD-10-CM Code
Transsexualism	F64.0
Dual role transvestism	F64.1
Gender identity disorder of childhood	F64.2
Other gender identity disorders	F64.8
Gender identity disorder, unspecified	F64.9

Cohort Construction-Terms Denoting Female-To-Male GAHT:

	ICD-10-CM/RXNORM/VA Class/HCPCS Code
Hormone replacement therapy	ICD10CM:Z79.890
ANDROGENS/ANABOLICS	VA:HS100
Testosterone	RXNORM:10379
Endocrine disorder, unspecified	ICD10CM:E34.9
Injection, testosterone cypionate, 1 mg	HCPCS:J1071
Injection, testosterone enanthate, 1 mg	HCPCS:J3121
Injection, testosterone undecanoate, 1 mg	HCPCS:J3145

Cohort Construction-Terms Denoting Male-To-Female GAHT

	ICD-10-CM/RXNORM/VA Class/HCPCS/ ATC Code
Hormone replacement therapy	ICD10CM:Z79.890
ESTROGENS	ATC:G03C
Estrogens	ATC:L02AA
Endocrine disorder, unspecified	ICD10CM:E34.9
ESTROGENS	VA:HS300
estrogens, esterified (USP)	RXNORM:214549
Estrogens	RXNORM:4100

Outcome Measures-Terms Denoting Gallbladder Disease

	ICD-10-CM Code
Cholelithiasis	ICD10CM:K80
Cholangitis	ICD10CM:K83.0
Cholecystitis	ICD10CM:K81
Obstruction of bile duct	ICD10CM:K83.1

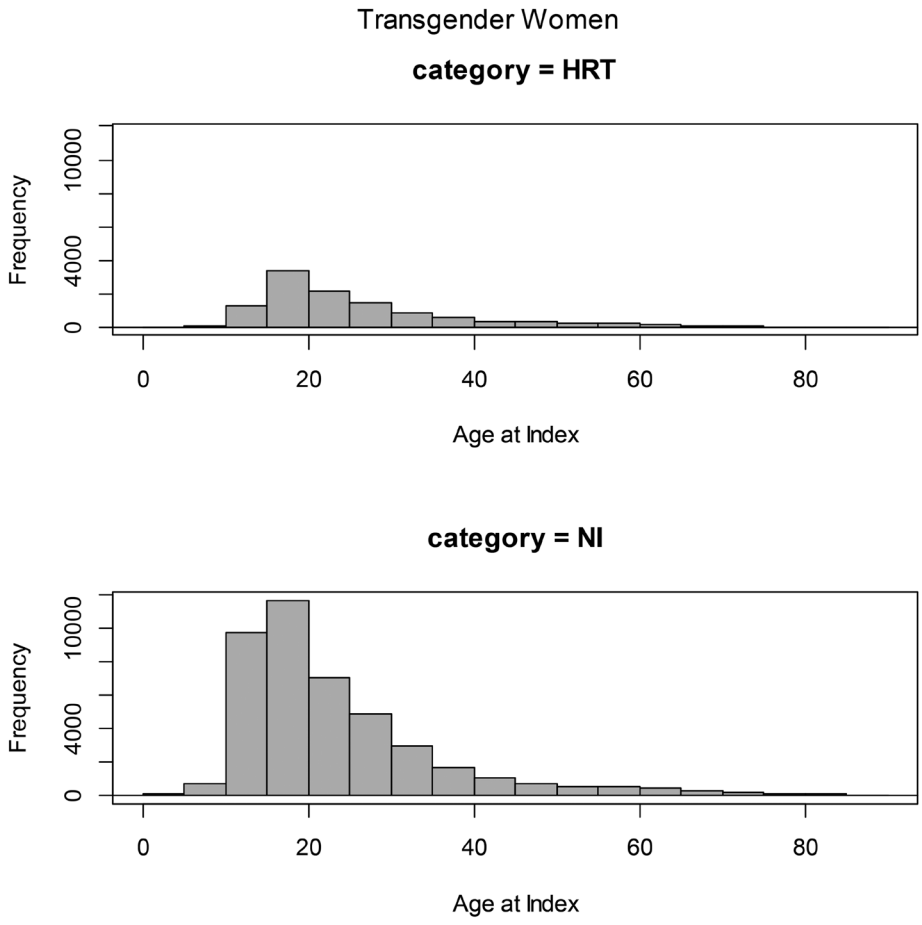
Outcome Measures-Terms Denoting Gallbladder Surgery

	CPT Code:
Cholecystectomy	1014153
Cholecystectomy with exploration of common duct	1014154
Laparoscopy, surgical; cholecystectomy	47562
Laparoscopy, surgical; cholecystectomy with cholangiography	47563
Laparoscopy, surgical; cholecystectomy with exploration of common duct	47564

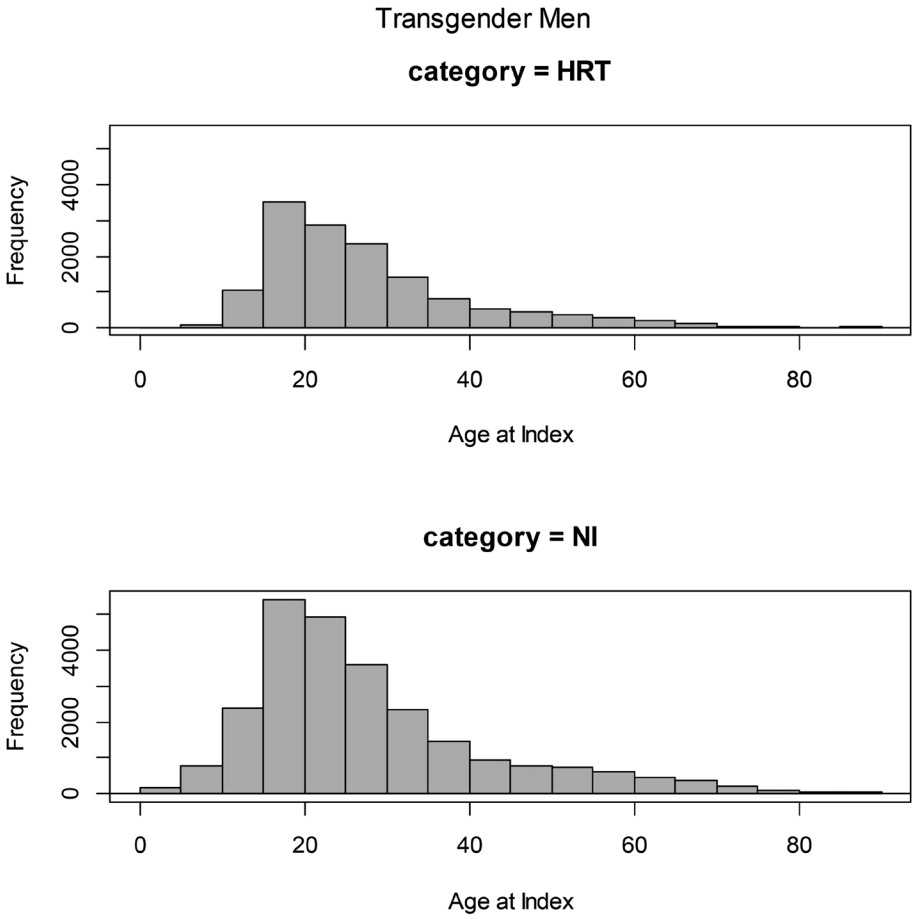
Appendix B. Cohort baseline characteristics and propensity score matching

Age histograms

1. Distribution of age at index of **transgender women**



2. Distribution of age at index of **transgender men**



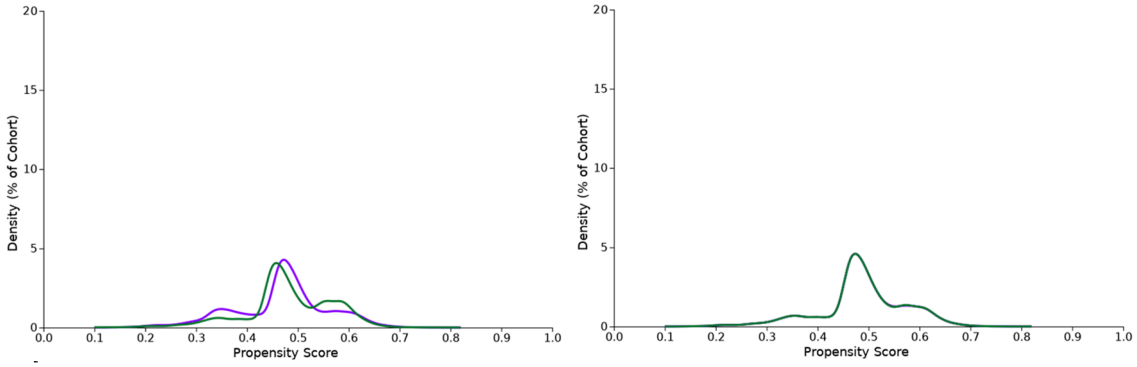
Balance tables

TWHT vs TWNI:

Cohort 1 and cohort 2 patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
1 - TWHT15+ No Biliary	20,188	15,900
2 - TWNI15 + No Biliary	17,926	15,900

Propensity score density function – Before and after matching (cohort 1 – purple, cohort 2 – green)



Cohort 1 ($N = 20,188$) and cohort 2 ($N = 17,926$) characteristics before propensity score matching

Demographics Cohort			Mean ± SD	Patients	% of Cohort	*p*-Value	Std diff.
1	Age	Current Age	32.2 ± 13.5	20,104	100%	.005	0.029
2			32.6 ± 15.2	17,735	100%		
1	AI	Age at Index	28.5 ± 13.0	20,104	100%	.271	0.011
2			28.7 ± 14.7	17,735	100%		

Continued.

1	2106-3	White	14,350	71.4%	<.001	0.130
2			11,591	65.4%		
1	UN	Unknown Ethnicity	3675	18.3%	<.001	0.202
2			4728	26.7%		
1	2186-5	Not Hispanic or Latino	14,818	73.7%	<.001	0.177
2			11,631	65.6%		
1	2135-2	Hispanic or Latino	1611	8.0%	.359	0.009
2			1376	7.8%		
1	2054-5	Black or African American	1682	8.4%	<.001	0.055
2			1767	10.0%		
1	M	Male	20,104	100%	--	--
2			17,735	100%		
1	2131-1	Unknown Race	3441	17.1%	<.001	0.107
2			3780	21.3%		
1	2028-9	Asian	398	2.0%	.299	0.011
2			378	2.1%		

Diagnosis Cohort			Mean ± SD	Patients	% of Cohort	*p*-Value	Std diff.
1	F10.1	Alcohol abuse		366	1.8%	.809	0.002
2				317	1.8%		
1	F10.2	Alcohol dependence		203	1.0%	.037	0.021
2				219	1.2%		
1	F17	Nicotine dependence		1510	7.5%	<.001	0.087
2				952	5.4%		
1	F17.2	Nicotine dependence		1510	7.5%	<.001	0.087
2				952	5.4%		
1	F17.20	Nicotine dependence,		1071	5.3%	<.001	0.080
2		unspecified		652	3.7%		
1	F17.21	Nicotine dependence,		712	3.5%	.012	0.026
2		cigarettes		546	3.1%		
1	E11	Type 2 diabetes mellitus		664	3.3%	.522	0.007
2				565	3.2%		
1	E10	Type 1 diabetes mellitus		202	1.0%	.170	0.014
2				154	0.9%		
1	E78.5	Hyperlipidemia, unspecified		964	4.8%	<.001	0.062
2				629	3.5%		
1	E78.4	Other hyperlipidemia		473	2.4%	<.001	0.038
2				320	1.8%		
1	E78.0	Pure hypercholesterolemia		349	1.7%	.002	0.032
2				237	1.3%		
1	E78.2	Mixed hyperlipidemia		318	1.6%	<.001	0.047
2				186	1.0%		
1	K74	Fibrosis and cirrhosis of liver		48	0.2%	.011	0.026
2				68	0.4%		
1	K70	Alcoholic liver disease		20	0.1%	.063	0.019
2				30	0.2%		
1	K76.0	Fatty (change of) liver, not		228	1.1%	.002	0.033
2		elsewhere classified		144	0.8%		
1	R63.4	Abnormal weight loss		350	1.7%	.015	0.025
2				253	1.4%		

Laboratory Cohort			Mean ± SD	Patients	% of Cohort	*p*-Value	Std diff.
1	9083	BMI	26.4 ± 6.9	6683	33.2%	.853	0.004
2			26.4 ± 7.2	3601	20.3%		
1		1–18.40 kg/m^2		1095	5.4%	<.001	0.040
2				810	4.6%		
1		18.50–24.90 kg/m^2		3506	17.4%	<.001	0.201
2				1864	10.5%		
1		25–29.90 kg/m^2		2330	11.6%	<.001	0.145
2				1306	7.4%		
1		30–39.90 kg/m^2		1854	9.2%	<.001	0.136
2				1003	5.7%		
1		40–99 kg/m^2		467	2.3%	<.001	0.053
2				282	1.6%		

Cohort 1 ($N = 15,900$) and cohort 2 ($N = 15,900$) characteristics after propensity score matching

Demographics Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	Age	Current Age	32.2 +± 13.6	15,900	100%	.277	0.012
2			32.4 ± 15.2	15,900	100%		
1	AI	Age at Index	28.5 ± 13.0	15,900	100%	.456	0.008
2			28.6 ± 14.7	15,900	100%		

Continued.

1	2106-3	White	10,949	68.9%	.725	0.004
2			10,978	69.0%		
1	UN	Unknown Ethnicity	3431	21.6%	.007	0.030
2			3,235	20.3%		
1	2186-5	Not Hispanic or Latino	11,193	70.4%	.070	0.020
2			11,340	71.3%		
1	2135-2	Hispanic or Latino	1276	8.0%	.316	0.011
2			1325	8.3%		
1	2054-5	Black or African American	1477	9.3%	.877	0.002
2			1485	9.3%		
1	M	Male	15,900	100%	--	--
2			15,900	100%		
1	2131-1	Unknown Race	2960	18.6%	.325	0.011
2			2892	18.2%		
1	2028-9	Asian	334	2.1%	.670	0.005
2			345	2.2%		

Diagnosis Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	F10.1	Alcohol abuse		253	1.6%	.293	0.012
2				277	1.7%		
1	F10.2	Alcohol dependence		165	1.0%	.869	0.002
2				168	1.1%		
1	F17	Nicotine dependence		897	5.6%	.942	0.001
2				900	5.7%		
1	F17.2	Nicotine dependence		897	5.6%	.942	0.001
2				900	5.7%		
1	F17.20	Nicotine dependence,		615	3.9%	.931	0.001
2		unspecified		618	3.9%		
1	F17.21	Nicotine dependence,		465	2.9%	.266	0.012
2		cigarettes		499	3.1%		
1	E11	Type 2 diabetes mellitus		498	3.1%	.654	0.005
2				512	3.2%		
1	E10	Type 1 diabetes mellitus		143	0.9%	.953	0.001
2				142	0.9%		
1	E78.5	Hyperlipidemia, unspecified		623	3.9%	.621	0.006
2				606	3.8%		
1	E78.4	Other hyperlipidemia		315	2.0%	.626	0.005
2				303	1.9%		
1	E78.0	Pure hypercholesterolemia		224	1.4%	.887	0.002
2				227	1.4%		
1	E78.2	Mixed hyperlipidemia		179	1.1%	.916	0.001
2				181	1.1%		
1	K74	Fibrosis and cirrhosis of liver		40	0.3%	.517	0.007
2				46	0.3%		
1	K70	Alcoholic liver disease		16	0.1%	.505	0.007
2				20	0.1%		
1	K76.0	Fatty (change of) liver, not		132	0.8%	.626	0.005
2		elsewhere classified		140	0.9%		
1	R63.4	Abnormal weight loss		250	1.6%	.616	0.006
2				239	1.5%		

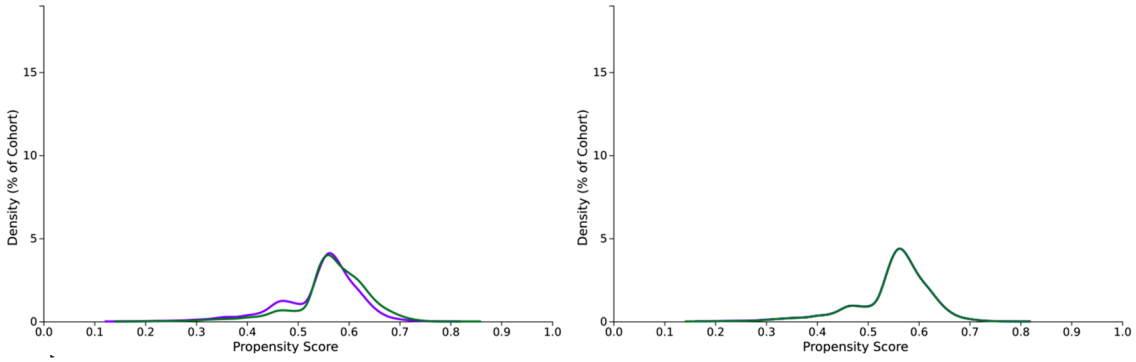
Laboratory Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	9083	BMI	26.2 ± 7.1	3957	24.9%	.123	0.036
2			26.4 ± 7.2	3530	22.2%		
1		1–18.40 kg/m2		799	5.0%	.453	0.008
2				770	4.8%		
1		18.50–24.90 kg/m2		1870	11.8%	.767	0.003
2				1853	11.7%		
1		25–29.90 kg/m2		1378	8.7%	.057	0.021
2				1284	8.1%		
1		30–39.90 kg/m2		1003	6.3%	.908	0.001
2				998	6.3%		
1		40–99 kg/m2		280	1.8%	.830	0.002
2				275	1.7%		

TMHT vs TMNI:

Cohort 1 and cohort 2 patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
1 - TMHT15 + No Biliary	22,786	21,406
2 - TMNI15 + NoBiliary	30,061	21,406

Propensity score density function – Before and after matching (cohort 1 – purple, cohort 2 – green)



Cohort 1 ($N = 22,786$) and cohort 2 ($N = 30,061$) characteristics before propensity score matching

Demographics							
Cohort			Mean ± SD	Patients	% of Cohort	*p*-Value	Std diff.
1	Age	Current Age	27.9 ± 11.7	22,764	100%	<.001	0.093
2			29.2 ± 14.6	29,864	100%		
1	AI	Age at Index	24.5 ± 11.2	22,764	100%	<.001	0.074
2			25.4 ± 13.9	29,864	100%		
1	2106-3	White		15,986	70.2%	<.001	0.052
2				20,257	67.8%		
1	UN	Unknown Ethnicity		4691	20.6%	<.001	0.105
2				7472	25.0%		
1	2186-5	Not Hispanic or Latino		16,205	71.2%	<.001	0.083
2				20,114	67.4%		
1	2135-2	Hispanic or Latino		1868	8.2%	.015	0.021
2				2278	7.6%		
1	2054-5	Black or African American		1555	6.8%	.166	0.012
2				2133	7.1%		
1	2131-1	Unknown Race		4494	19.7%	<.001	0.050
2				6500	21.8%		
1	2028-9	Asian		518	2.3%	.846	0.002
2				672	2.3%		
Diagnosis							
Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	F10.1	Alcohol abuse		250	1.1%	.003	0.026
2				252	0.8%		
1	F10.2	Alcohol dependence		154	0.7%	.008	0.023
2				149	0.5%		
1	F17	Nicotine dependence		1208	5.3%	<.001	0.117
2				892	3.0%		
1	F17.20	Nicotine dependence, unspecified		751	3.3%	<.001	0.088
2				566	1.9%		
1	F17.21	Nicotine dependence, cigarettes		609	2.7%	<.001	0.073
2				482	1.6%		
1	E11	Type 2 diabetes mellitus		590	2.6%	.028	0.019
2				685	2.3%		
1	E10	Type 1 diabetes mellitus		210	0.9%	.167	0.012
2				242	0.8%		
1	K74	Fibrosis and cirrhosis of liver		38	0.2%	.384	0.008
2				41	0.1%		
1	K70	Alcoholic liver disease		10	0.0%	.514	0.006
2				17	0.1%		
1	K76.0	Fatty (change of) liver, not elsewhere classified		191	0.8%	.001	0.028
2				179	0.6%		
1	R63.4	Abnormal weight loss		446	2.0%	.127	0.013
2				531	1.8%		
1	E78.1	Pure hyperglyceridemia		182	0.8%	.001	0.029
2				168	0.6%		

Continued.

1	E78.2	Mixed hyperlipidemia		284	1.2%	<.001	0.049
2				226	0.8%		
1	E78.4	Other hyperlipidemia		329	1.4%	.056	0.017
2				374	1.3%		
1	E78.5	Hyperlipidemia, unspecified		793	3.5%	<.001	0.054
2				766	2.6%		

Laboratory

Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	9083	BMI	27.5 ± 7.7	8051	35.4%	<.001	0.149
2			26.4 ± 7.5	6949	23.3%		
1		1–18.40 kg/m^2		1433	6.3%	.718	0.003
2				1857	6.2%		
1		18.50–24.90 kg/m^2		4200	18.5%	<.001	0.147
2				3918	13.1%		
1		25–29.90 kg/m^2		2776	12.2%	<.001	0.137
2				2408	8.1%		
1		30–39.90 kg/m^2		2510	11.0%	<.001	0.163
2				1924	6.4%		
1		40–99 kg/m^2		858	3.8%	<.001	0.108
2				586	2.0%		

Cohort 1 ($N = 21{,}406$) and cohort 2 ($N = 21{,}406$) characteristics after propensity score matching

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	Age	Current Age	28.0 ± 11.8	21,406	100%	.344	0.009
2			27.8 ± 13.0	21,406	100%		
1	AI	Age at Index	24.5 ± 11.3	21,406	100%	.613	0.005
2			24.5 ± 12.6	21,406	100%		
1	2106-3	White		14,998	70.1%	.363	0.009
2				15,084	70.5%		
1	UN	Unknown Ethnicity		4558	21.3%	.001	0.033
2				4272	20.0%		
1	2186-5	Not Hispanic or Latino		15,121	70.6%	.077	0.017
2				15,287	71.4%		
1	2135-2	Hispanic or Latino		1727	8.1%	.036	0.020
2				1847	8.6%		
1	2054-5	Black or African American		1453	6.8%	.350	0.009
2				1502	7.0%		
1	2131-1	Unknown Race		4271	20.0%	.054	0.019
2				4113	19.2%		
1	2028-9	Asian		483	2.3%	.213	0.012
2				522	2.4%		

Diagnosis

Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	F10.1	Alcohol abuse		212	1.0%	.844	0.002
2				208	1.0%		
1	F10.2	Alcohol dependence		134	0.6%	.805	0.002
2				130	0.6%		
1	F17	Nicotine dependence		961	4.5%	.034	0.021
2				872	4.1%		
1	F17.20	Nicotine dependence, unspecified		592	2.8%	.231	0.012
2				552	2.6%		
1	F17.21	Nicotine dependence, cigarettes		479	2.2%	.793	0.003
2				471	2.2%		
1	E11	Type 2 diabetes mellitus		529	2.5%	.572	0.005
2				511	2.4%		
1	E10	Type 1 diabetes mellitus		196	0.9%	.919	0.001
2				198	0.9%		
1	K74	Fibrosis and cirrhosis of liver		30	0.1%	.691	0.004
2				27	0.1%		
1	K70	Alcoholic liver disease		10	0.0%	1	<0.001
2				10	0.0%		
1	K76.0	Fatty (change of) liver, not elsewhere classified		168	0.8%	.401	0.008
2				153	0.7%		
1	R63.4	Abnormal weight loss		411	1.9%	.861	0.002
2				416	1.9%		
1	E78.1	Pure hyperglyceridemia		161	0.8%	.531	0.006
2				150	0.7%		
1	E78.2	Mixed hyperlipidemia		228	1.1%	.336	0.009
2				208	1.0%		

Continued.

1	E78.4	Other hyperlipidemia		291	1.4%	.674	0.004
2				281	1.3%		
1	E78.5	Hyperlipidemia,		666	3.1%	.675	0.004
2		unspecified		651	3.0%		

Laboratory Cohort			Mean ± SD	Patients	% of Cohort	*p*-value	Std diff.
1	9083	BMI	27.2 ± 7.7	6847	32.0%	.007	0.047
2			26.9 ± 7.5	6283	29.4%		
1		1–18.40 kg/m^2		1361	6.4%	.127	0.015
2				1439	6.7%		
1		18.50–24.90 kg/m^2		3495	16.3%	.003	0.028
2				3722	17.4%		
1		25–29.90 kg/m^2		2346	11.0%	.207	0.012
2				2265	10.6%		
1		30–39.90 kg/m^2		2012	9.4%	.021	0.022
2				1875	8.8%		
1		40–99 kg/m^2		680	3.2%	.003	0.029
2				575	2.7%		