

Sex disparities in gallstone disease: insights from the MAUCO

Prospective Population-Based Cohort Study

SUPPLEMENTARY FILES

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Supplementary Figure S1. Diagram of participants included in the study.

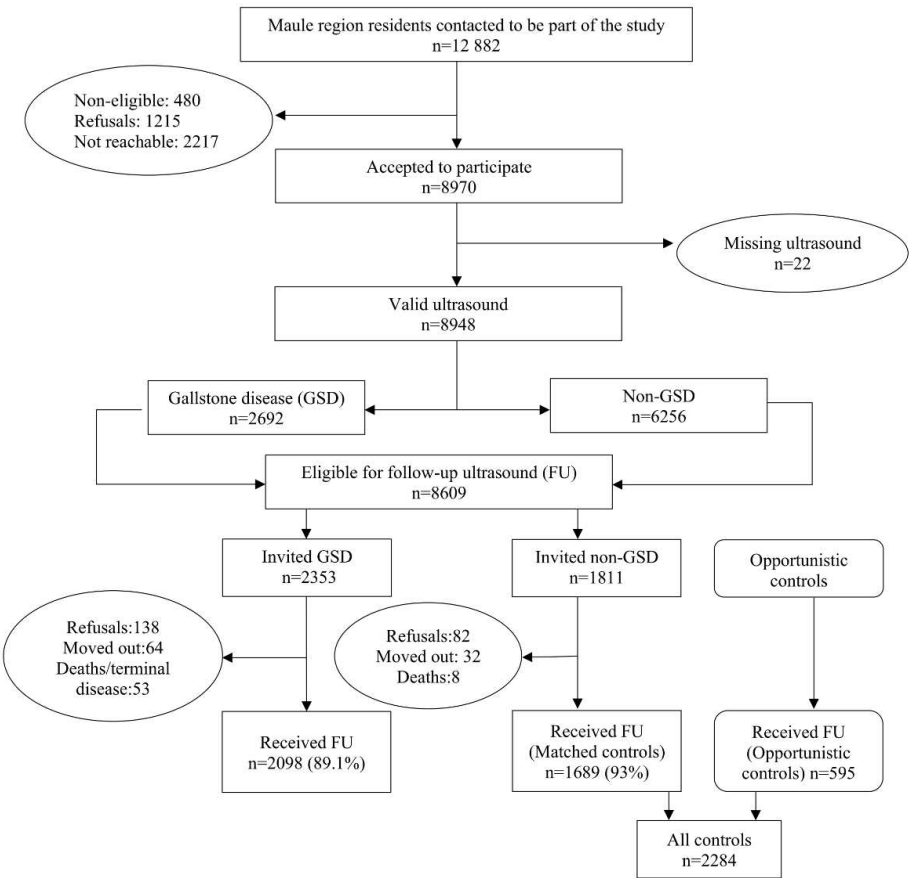


Table S1. Distribution of missing variables at baseline characteristics of women and men by gallstone disease status (n=8774). MAUCO 2015-2019.

Baseline characteristics	Women (n=4838)		Men (n=3936)	
	Non-GSD (n=2848)	GSD (n=1990)	Non-GSD (n=3234)	GSD (n=702)
	%	%	%	%
Age	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Above 8 years of schooling	2 (0.07)	3 (0.15)	3 (0.09)	1 (0.14)
Low healthcare coverage ^a	17 (0.60)	10 (0.50)	17 (0.53)	4 (0.57)
Chilean-Hispanic ancestry	24 (0.84)	12 (0.60)	13 (0.40)	4 (0.57)
Less than 20 remaining teeth	13 (0.46)	9 (0.45)	18 (0.57)	5 (0.71)
Mediterranean Diet Score ≥ 9	167 (5.86)	128 (6.43)	149 (4.61)	35 (4.99)
High-fat red meat >2 t/w	76 (2.67)	66 (3.32)	50 (1.55)	13 (1.85)
Sugary drinks >2 t/d	48 (1.69)	50 (2.51)	30 (0.93)	9 (1.28)
Whole grains >3 t/w	141 (4.95)	104 (5.23)	119 (3.68)	27 (3.85)
Legumes >1 t/w	11 (0.38)	11 (0.55)	15 (0.46)	1 (0.14)
Fruit intake ≥ 1 t/d	3 (0.11)	5 (0.25)	6 (0.18)	0 (0.00)
Vegetable intake ≥ 1 t/d	6 (0.21)	8 (0.40)	10 (0.31)	4 (0.57)
Risky alcohol intake	43 (1.51)	31 (1.56)	58 (1.79)	9 (1.28)
Ever smoker	20 (0.70)	17 (0.85)	26 (0.80)	4 (0.57)
Current smoker	36 (1.26)	37 (1.86)	43 (1.33)	11 (1.57)
Low physical activity ^b	24 (0.84)	31 (1.56)	31 (0.96)	11 (1.57)
Low grip strength ^c	33 (1.16)	26 (1.31)	29 (0.90)	10 (1.42)
Slow walking pace ^d	754 (26.47)	544 (27.33)	613 (18.95)	133 (18.95)
Children 3 and more	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hormone contraception, ever	9 (0.32)	6 (0.30)	-	-
HRT, ever	37 (1.30)	21 (1.06)	-	-
Family history of gallstones	116 (4.07)	75 (3.77)	121 (3.74)	27 (3.85)
Family history of GBC	5 (0.18)	3 (0.15)	12 (0.37)	4 (0.57)
High body fat ^e	60 (2.11)	36 (1.81)	189 (5.84)	32 (4.56)
Abdominal obesity ^f	8 (0.28)	2 (0.10)	13 (0.40)	1 (0.14)
BMI ≥ 30 kg/m ²	7 (0.25)	1 (0.05)	3 (0.09)	0 (0.00)
LDL ≥ 160 mg/dL	34 (1.19)	34 (1.71)	113 (3.49)	30 (4.27)
Low HDL ^g	9 (0.32)	6 (0.30)	11 (0.34)	3 (0.43)
Triglycerides ≥ 200 mg/dL	10 (0.35)	6 (0.30)	10 (0.31)	3 (0.43)
Current use of statins	300 (10.53)	218 (10.95)	342 (10.57)	75 (10.68)
Bilirubin Total >1.2 mg/dL	12 (0.42)	6 (0.30)	12 (0.37)	4 (0.57)
Bilirubin Direct >0.3 mg/dL	11 (0.39)	5 (0.25)	15 (0.46)	5 (0.71)
AST ≥ 48 IU/L	11 (0.39)	5 (0.25)	11 (0.34)	3 (0.43)
ALT ≥ 55 IU/L	11 (0.39)	6 (0.30)	12 (0.37)	3 (0.43)
ALT/AST ≥ 1.33	11 (0.39)	6 (0.30)	12 (0.37)	3 (0.43)
ALP >129 IU/L	11 (0.39)	5 (0.25)	11 (0.34)	3 (0.43)
Fatty liver	5 (0.18)	2 (0.10)	6 (0.19)	1 (0.14)
Biliary colic	15 (0.53)	15 (0.75)	12 (0.37)	7 (0.99)

Dyspepsia	38 (1.33)	13 (0.65)	40 (1.24)	6 (0.85)
Diabetes	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
High blood pressure	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Cardiovascular disease	10 (0.35)	10 (0.50)	8 (0.25)	4 (0.57)
Metabolic Syndrome	15 (0.53)	9 (0.45)	24 (0.74)	5 (0.71)

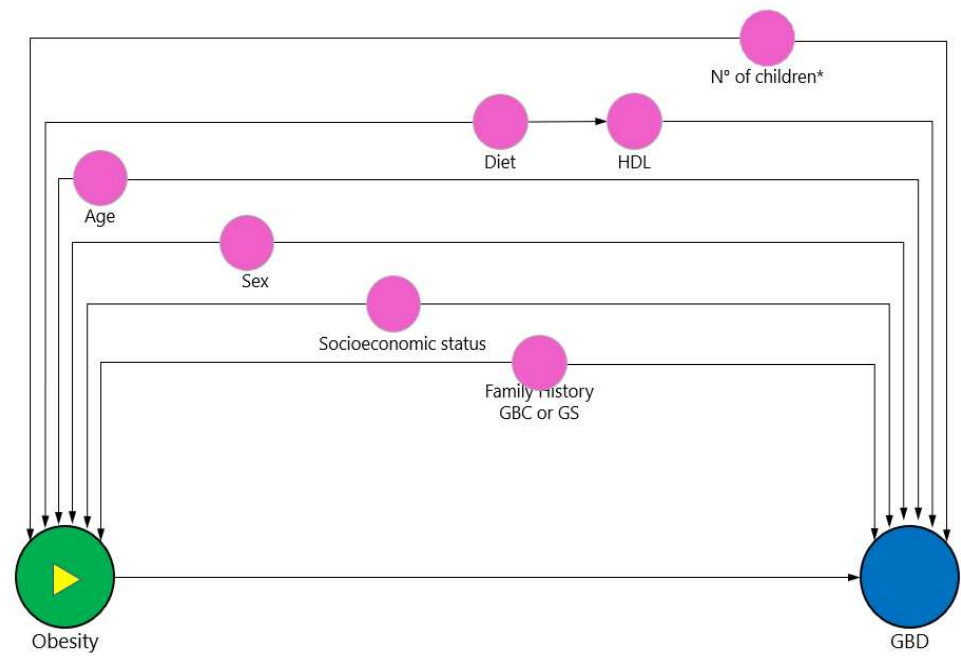
Other gallbladder anomalies (n=174) excluded. Abbreviations: GSD, gallstone disease; GBC, gallbladder cancer; HRT, hormone replacement therapy; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; t/w, times per week; t/d, times per day. ^aPublic levels A or B. ^b< 3 times per week (30 minutes each time).^c Low grip strength <16 kg in women, <27 kg in men. ^d Self-reported slow walking pace. ^e Waist circumference ≥88 cm in women and ≥102 cm in men. ^f <50 mg/dL in women and <40 mg/dL in men.

Table S2. All gallbladder anomalies and biliary colic at baseline ultrasound. MAUCO 2015-2019.

	Frequency (%)			
Baseline ultrasound findings	All n=8948	Women n=4918	Men n=4030	<i>p-value</i> ^a
A.Gallbladder anomalies at baseline ultrasound.				
Gallstone disease	2692 (30.0)	1990 (40.4)	702 (17.1)	<0.001
Other gallbladder anomalies	174 (1.9)	80 (1.6)	94 (2.3)	0.016
Polyps	134 (1.5)	59 (1.2)	75 (1.9)	0.010
Scleroatrophic gallbladder	57 (0.6)	32 (0.7)	25 (0.6)	0.858
Wall thickening	41 (0.6)	24 (0.7)	17 (0.5)	0.219
Cholesterolosis	40 (0.5)	16 (0.3)	24 (0.6)	0.057
Wall calcifications	21 (0.3)	12 (0.3)	9 (0.2)	0.461
Image suggestive of neoplasm	9 (0.1)	5 (0.1)	4 (0.1)	0.971
Adenomyomatosis	4 (0.0)	2 (0.0)	2 (0.0)	0.842
Adenomyosis	3 (0.0)	0 (0.0)	3 (0.0)	0.056
B.Biliary Colic at enrolment by gallbladder status at baseline.*				
Normal	722 (60.5)	495 (56.1)	227 (72.9)	<0.001
Gallstones	214 (17.9)	155 (17.6)	59 (19.0)	0.641
Cholecystectomy	257 (21.5)	232 (26.3)	25 (8.0)	<0.001

Gallstone disease: gallstones, biliary sludge, or cholecystectomy. ^a*p* values for sex differences from the Chi-square test with Yates' continuity correction. *Percentages were obtained from total of biliary colic; 1193 All, 882 Women and 311 Men.

Supplementary Figure S2. Directed acyclic graph of obesity effect on GBD



Abbreviature, SES: Socioeconomic status, GBD: Gallbladder disease ;*Only women

Table S3. Baseline characteristics of women and men by GSD status (n=8774). MAUCO 2015-2019.

Baseline characteristics	Women (n=4838)		Men (n=3936)	
	Non-GSD (n=2848)	GSD (n=1990)	Non-GSD (n=3234)	GSD (n=702)
	%	%	%	%
Age, years 38-44	801 (28.1)	302 (15.2)	799 (24.7)	77 (11.0)
45-54	1042 (36.6)	623 (31.3)	1070 (33.1)	175 (24.9)
55-64	681 (23.9)	638 (32.1)	913 (28.2)	230 (32.8)
65-74	324 (11.4)	427 (21.5)	452 (14.0)	220 (31.3)
Above 8 years of schooling	1589 (55.8)	885 (44.5)	1671 (51.7)	351 (50.1)
Low healthcare coverage ^a	2117 (74.8)	1607 (81.2)	2331 (72.5)	511 (73.2)
Chilean-Hispanic ancestry	2773 (97.9)	1944 (98.1)	3137 (97.3)	682 (97.7)
Less than 20 remaining teeth	1140 (40.2)	1105 (55.8)	1352 (42.0)	358 (51.4)
Mediterranean Diet Score ≥ 9	66 (2.5)	32 (1.7)	28 (0.9)	6 (0.9)
High-fat red meat >2 t/w	262 (9.5)	141 (7.3)	371 (11.7)	67 (9.7)
Sugary drinks >2 t/d	267 (9.5)	164 (8.5)	639 (19.9)	116 (16.7)
Whole grains >3 t/w	547 (20.2)	326 (17.3)	267 (8.6)	63 (9.3)
Legumes >1 t/w	2374 (83.7)	1628 (82.3)	2714 (84.3)	590 (84.3)
Fruit intake ≥ 1 t/d	1640 (57.6)	1066 (53.7)	1419 (44.0)	329 (46.9)
Vegetable intake ≥ 1 t/d	2117 (74.5)	1434 (72.4)	1950 (60.5)	418 (59.9)
Risky alcohol intake	321 (11.4)	152 (7.8)	1001 (31.5)	170 (24.5)
Ever smoker	1472 (52.1)	1008 (51.1)	2087 (65.1)	459 (65.8)
Current smoker	873 (31.0)	575 (29.4)	1124 (35.2)	194 (28.1)
Low physical activity ^b	2590 (91.7)	1831 (93.5)	2979 (93.0)	631 (91.3)
Low grip strength ^c	320 (11.4)	274 (14.0)	366 (11.4)	84 (12.1)
Slow walking pace ^d	532 (25.4)	440 (30.4)	464 (17.7)	152 (26.7)
Children 3 and more	1251 (43.9)	1071 (53.8)	-	-
Hormone contraception, ever	1690 (59.5)	1050 (52.9)	-	-
HRT, ever	351 (12.5)	288 (14.6)	-	-
Family history of gallstones	1407 (51.5)	1156 (60.4)	1132 (36.4)	333 (49.3)
Family history of GBC	58 (2.0)	57 (2.9)	20 (0.6)	12 (1.7)
Abdominal obesity ^e	2178 (76.7)	1716 (86.3)	1428 (44.3)	388 (55.3)
BMI ≥ 30 kg/m ²	1075 (37.8)	996 (50.1)	1166 (36.1)	299 (42.6)
LDL ≥ 160 mg/dL	324 (11.5)	189 (9.7)	314 (10.1)	44 (6.5)
Low HDL ^f	1651 (58.2)	1208 (60.9)	1251 (38.8)	322 (46.1)
Triglycerides ≥ 200 mg/dL	544 (19.2)	477 (24.0)	951 (29.5)	219 (31.3)
Current use of statins	215 (8.4)	216 (12.2)	140 (4.8)	46 (7.3)
Bilirubin Total >1.2 mg/dL	62 (2.2)	50 (2.5)	211 (6.5)	55 (7.9)
Bilirubin Direct >0.3 mg/dL	85 (3.0)	89 (4.5)	203 (6.3)	62 (8.9)
AST ≥ 48 IU/L	126 (4.4)	118 (5.9)	228 (7.1)	58 (8.3)
ALT ≥ 55 IU/L	193 (6.8)	185 (9.3)	499 (15.5)	106 (15.2)
ALT/AST ≥ 1.33	391 (13.8)	223 (11.2)	242 (7.5)	58 (8.3)
ALP >129 IU/L	276 (9.7)	287 (14.5)	208 (6.5)	65 (9.3)
Fatty liver Mild	799 (28.1)	691 (34.8)	905 (28.0)	222 (31.7)

Moderate	336 (11.8)	387 (19.5)	517 (16.0)	149 (21.3)
Severe	33 (1.2)	29 (1.5)	43 (1.3)	5 (0.7)
Biliary colic	495 (17.5)	387 (19.6)	227 (7.0)	84 (12.1)
Dyspepsia	920 (32.7)	671 (33.9)	534 (16.7)	134 (19.3)
Diabetes	320 (11.2)	409 (20.6)	439 (13.6)	147 (20.9)
Hypertension	1308 (45.9)	1167 (58.6)	1929 (59.6)	470 (67.0)
Cardiovascular disease	167 (5.9)	151 (7.6)	207 (6.4)	77 (11.0)
Metabolic Syndrome	1300 (45.9)	1153 (58.2)	1391 (43.3)	377 (54.1)

Other gallbladder anomalies (n=174) excluded. Abbreviations: GSD, gallstone disease; GBC, gallbladder cancer; HRT, hormone replacement therapy; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; t/w, times per week; t/d, times per day. ^aPublic levels A or B. ^b< 3 times per week (30 minutes each time).^c Low grip strength <16 kg in women, <27 kg in men. ^d Self-reported slow walking pace. ^e Waist circumference ≥88 cm in women and ≥102 cm in men. ^f <50 mg/dL in women and <40 mg/dL in men.

Table S4. Comparison of gallstone disease participants and matched and opportunistic non-GSD controls.

Baseline characteristics	GSD			Non-GSD				
				Matched control		Opportunistic control		
	Invited (n=2353)	Attended (n=2098)	<i>p</i> -value ^a	Invited (n=1811)	Attended (n=1689)	<i>p</i> -value ^b	(n=595)	<i>p</i> -value ^c
Sex, women	74.8	76.0	0.38	69.9	70.1	0.90	52.1	<0.001
Age, years								
38-44	13.8	13.6		15.5	15.4		30.5	
45-54	29.6	30.7	0.71	31.3	31.9	0.92	42.5	<0.001
55-64	32.7	33.1		32.8	33.1		20.6	
65-74	23.9	22.6		20.5	19.6		6.4	
> 8 years of schooling	60.8	61.6	0.63	63.3	64.1	0.65	80.9	<0.001
Low healthcare coverage ^d	78.7	78.1	0.66	76.2	76.4	0.93	69.0	0.002
Chilean-Hispanic	98.0	98.0	0.99	97.8	97.7	0.99	97.8	0.97
< 20 remaining teeth	56.2	55.7	0.74	53.2	52.6	0.72	32.0	<0.001
Risky alcohol intake	3.9	3.6	0.85	3.3	3.5	0.91	3.1	0.98
Ever smoker	54.9	54.5	0.81	56.8	57.2	0.81	59.7	0.23
Family history of gallstones	56.7	57.6	0.57	47.3	47.9	0.72	48.7	0.59
Family history of GBC	2.3	2.5	0.83	2.0	2.1	0.86	1.7	0.76
High body fat ^e	88.2	88.2	0.99	81.3	81.1	0.93	75.9	0.006
Abdominal obesity ^f	78.3	78.9	0.70	69.3	69.4	0.99	64.0	0.02
BMI ≥ 30 kg/m ²	48.2	48.6	0.82	36.4	36.4	0.99	42.4	0.01
Low HDL ^g	58.5	58.9	0.81	54.1	53.9	0.94	50.8	0.16
Fatty liver								
Mild	35.9	36.9		31.9	32.0		27.0	
Moderate/Severe	20.4	20.2	0.89	14.1	14.1	0.99	21.1	<0.001
Biliary colic	18.4	18.2	0.88	15.4	15.7	0.82	12.6	0.11
Diabetes	19.3	18.2	0.36	14.1	13.6	0.75	7.4	<0.001
High blood pressure	65.6	65.2	0.82	60.5	59.7	0.65	53.8	0.004
Cardiovascular disease	8.7	8.0	0.48	8.2	7.9	0.75	4.7	0.005
Metabolic Syndrome	57.3	57.6	0.88	48.2	47.7	0.76	44.2	0.098
Incident GSD*				8.2	8.2	0.99	6.2	0.3

p-values calculated with Chi-square test with Yates' continuity correction. ^a GSD invited versus attended; ^b Matched controls invited versus attended; ^c Opportunistic versus matched controls. Abbreviations: GSD, gallstone disease; HDL, high-density lipoprotein; GBC, gallbladder cancer; US, ultrasound. ^d Participant with public health insurance level A or B. ^e Measured by bioimpedance analysis as >35% in women and >25% in men. ^f Waist circumference ≥ 88 cm in women and ≥ 102 cm in men. ^g <50 mg/dL in women and <40 mg/dL in men. * This is the only information estimated during the follow-up and that was used for creating the following Supplementary Tables.

Table S5. GSD-associated factors at baseline ultrasound by sex, age-adjusted. MAUCO 2015-2019.

Baseline factors (reference category)	Women with GSD			Men with GSD		
	Denominator N:4838	n (%) n:1990(41.4)	Age-adjust PRR (95% CI)	Denominator N: 3936	n (%) 702(17.8)	Age-adjust PRR (95% CI)
45-54 (38-44)	1665	623 (37.4)	1.37 (1.22-1.53)	1245	175 (14.1)	1.60 (1.24-2.06)
55-64	1319	638 (48.4)	1.77 (1.58-1.97)	1143	230 (20.1)	2.29 (1.80-2.92)
65-74	751	427 (56.9)	2.08 (1.85-2.32)	672	220 (32.7)	3.72 (2.93-4.73)
Schooling ≤8 years	2359	1102 (46.7)	1.17 (1.09-1.26)	1910	351 (18.3)	0.86 (0.75-0.98)
Low healthcare coverage ^a	3724	1607 (43.2)	1.16 (1.06-1.27)	2842	511 (21.9)	0.88 (0.76-1.02)
Less than 20 remaining teeth	2245	1105 (49.2)	1.18 (1.09-1.28)	1710	358 (20.9)	0.89 (0.77-1.04)
Mediterranean Diet Score ≥9	98	32 (32.7)	0.72 (0.55-0.96)	34	6 (17.6)	0.94 (0.46-1.92)
Fruit intake ≥1 time/day	2706	1066 (39.4)	0.87 (0.82-0.93)	1748	329 (18.8)	1.02 (0.89-1.16)
Ever smoker ^b	2480	1008 (40.6)	1.00 (0.94-1.07)	2546	459 (18.0)	1.07 (0.93-1.23)
Low grip strength ^c	594	274 (46.1)	1.05 (0.95-1.15)	450	84 (18.7)	0.83 (0.68-1.02)
Slow walking pace ^d	972	440 (45.3)	1.09 (0.99-1.18)	616	152 (24.6)	1.24 (1.05-1.47)
Three and more children	2322	1071 (46.1)	1.16 (1.09-1.24)	-	-	-
Family history of gallstones	2563	1156 (45.1)	1.23 (1.15-1.34)	1465	333 (22.7)	1.60 (1.40-1.82)
Family history of GBC	115	57 (49.6)	1.17 (0.97-1.40)	32	12 (37.5)	1.93 (1.27-2.95)
Abdominal obesity ^f	3894	1716 (44.1)	1.45 (1.31-1.61)	1816	388 (21.4)	1.36 (1.19-1.55)
Body Mass Index ≥30 kg/m ²	2071	996 (48.1)	1.32 (1.24-1.41)	1465	299 (20.4)	1.30 (1.14-1.48)
LDL ≥160 mg/dL	513	189 (36.8)	0.85 (0.76-0.96)	358	44 (12.3)	0.72 (0.55-0.96)
Low HDL ^g	2859	1208 (42.3)	1.09 (1.01-1.16)	1573	322 (20.5)	1.31 (1.15-1.50)
Triglycerides ≥200 mg/dL	1944	874 (45.0)	1.13 (1.06-1.21)	1170	219 (18.7)	1.18 (1.02-1.35)
Biliary colic	882	387 (43.8)	1.11 (1.03-1.21)	311	84 (27.0)	1.64 (1.35-1.99)
Dyspepsia	1591	671 (42.2)	1.04 (0.97-1.12)	668	134 (20.1)	1.22 (1.03-1.44)
Current use of statins	431	216 (50.1)	1.05 (0.95-1.17)	186	46 (24.7)	1.08 (0.84-1.39)
Fatty liver Mild (none)	1490	691 (46.4)	1.29 (1.19-1.39)	1127	222 (19.7)	1.28 (1.10-1.49)
Moderate	723	387 (53.5)	1.48 (1.36-1.61)	666	149 (22.4)	1.55 (1.30-1.83)
Severe	62	29 (46.8)	1.40 (1.08-1.81)	48	5 (10.4)	0.79 (0.35-1.80)
Total bilirubin >1.2 mg/dL	112	50 (44.6)	1.06 (0.87-1.28)	266	55 (20.7)	1.13 (0.89-1.43)
Direct bilirubin >0.3 mg/dL	174	89 (51.1)	1.18 (1.02-1.36)	265	62 (23.4)	1.18 (0.94-1.48)
AST ≥48 IU/L	244	118 (48.4)	1.18 (1.03-1.35)	286	58 (20.3)	1.28 (1.01-1.61)
ALT ≥55 IU/L	378	185 (48.9)	1.25 (1.12-1.39)	605	106 (17.5)	1.23 (1.02-1.48)
ALT/AST ≥1.33	1002	468 (46.7)	1.21 (1.12-1.31)	1494	251 (16.8)	1.16 (1.01-1.34)
Diabetes	729	409 (56.1)	1.30 (1.20-1.40)	558	140 (25.1)	1.26 (1.01-1.48)
Hypertension	2475	1167 (47.2)	1.15 (1.07-1.24)	2728	524 (19.2)	1.03 (0.88-1.21)
Cardiovascular disease*	318	151 (47.5)	1.03 (0.91-1.16)	284	77 (27.1)	1.30 (1.06-1.59)
Metabolic Syndrome	2453	1153 (47.0)	1.23 (1.15-1.32)	1768	376(21.3)	1.32 (1.16-1.51)

Poisson Multiple regression with robust variance age-adjusted. Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence intervals; GBC, gallbladder cancer; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRR, prevalence rate ratios. ^a Public health insurance level A or B. ^b Self-reported ever smoked ≥100 cigarettes. ^c Low grip strength: <16 kg in women <27 kg in men. ^d Self-reported slow walking pace. ^e Bioimpedance >35% women, >25% men. ^f Waist circumference ≥88 cm women, ≥102 cm men. ^g <50 mg/dL women <40 mg/dL men. *: Self-reported heart attack, vascular accident, or heart failure

Table S6. Risk factors of GSD incidence by type of controls. MAUCO 2015-2023.

	Total	New GBD	Person-years	Incidence 1000/p-y	Age-sex adjusted HR(95% CI)
A. Model with all controls (n=2284)					
Age, <45 years	287	26	1108.98	23.45	Ref
45-54 years	632	58	1912.99	30.32	1.48 (0.92-2.35)
55-64	830	60	2239.35	26.79	1.60 (1.005-2.56)
65+	535	54	1433.0	37.68	2.66 (1.64-4.31)
Men	789	59	2534.78	23.28	Ref
Women	1495	139	4159.53	33.41	1.81 (1.33-2.47)
Schooling +13 years	264	23	783.97	29.34	Ref
<4 years	243	18	693.48	25.96	0.84 (0.46-1.58)
4-8 years	864	83	2461.17	33.72	1.17 (0.74-1.88)
9-12 years	913	74	2755.69	26.85	0.96 (0.60-1.54)
Normal waist circumference	799	50	2484.57	20.12	Ref
Risk waist circumference*	1481	148	4198.94	35.24	1.65 (1.18-2.31)
Diet Med Score < 6	1406	114	4167.53	27.35	Ref
≥6	688	61	2007.62	30.38	1.91 (0.80-1.49)
HDL cholesterol ≥50,	1058	76	3150.33	24.12	Ref
<50	1221	121	3526.89	34.31	1.55 (1.16-2.06)
Family hist. GBC, No	2233	191	6556.0	29.13	Ref
Yes	46	6	124.75	48.1	1.63 (0.72-3.68)
B. Model with age-sex matched controls (n=1589)					
Age, <45 years	157	17	423.0	40.19	Ref
45-54 years	419	41	1045.51	39.21	1.02 (0.58-1.80)
55-64	627	48	1528.70	31.40	0.85 (0.49-1.48)
65+	486	51	1225.87	41.60	1.14 (0.66-1.98)
Men	505	42	1315.23	31.93	Ref
Women	1184	115	2907.84	39.55	1.32 (0.99-2.03)
Schooling +13 years	167	18	414.34	43.44	Ref
<4 years	205	16	510.73	31.33	0.78 (0.39-1.53)
4-8 years	682	69	1710.82	40.33	0.98 (0.58-1.66)
9-12 years	635	54	1587.19	34.02	0.82 (0.48-1.40)
Normal waist circumference	571	38	1479.92	25.68	Ref
Risk waist circumference*	1114	119	2732.35	43.55	1.83 (1.25-2.68)
Diet Med Score < 6	1019	89	2551.94	34.88	Ref
≥6	501	47	1249.66	37.61	1.03 (0.72-1.48)
HDL cholesterol ≥50,	770	59	1942.24	30.38	Ref
<50	916	97	2270.94	42.71	1.46 (1.05-2.01)
Family hist. GBC, No	1650	150	4135.93	36.27	Ref
Yes	36	6	80.86	74.20	2.74 (1.21-6.24)
C. Model with opportunistic controls (n=595)					

Age, <45 years	130	9	685.98	13.12	Ref
45-54 years	213	17	867.48	19.60	1.38 (0.61-3.11)
55-64	203	12	710.65	16.89	1.56 (0.64-3.81)
65+	49	3	207.13	14.48	2.98 (0.75-11.78)
Men	284	17	1219.56	13.94	Ref
Women	311	24	1251.69	19.17	1.62 (0.82-3.20)
Schooling +13 years	97	5	369.63	13.53	Ref
<4 years	38	2	182.76	10.94	0.56 (0.11-2.95)
4-8 years	182	14	750.35	18.66	0.96 (0.33-2.73)
9-12 years	278	20	1168.51	17.12	0.98 (0.36-2.67)
Normal waist circumference	228	12	1004.65	11.94	Ref
Risk waist circumference*	367	29	1466.59	19.77	1.36 (0.65-2.83)
Diet Med Score < 6	387	25	1615.59	15.47	Ref
≥6	187	14	757.96	18.47	1.28 (0.66-2.49)
HDL cholesterol ≥50	288	17	1208.09	14.07	Ref
<50	305	24	1255.95	19.10	1.57 (0.83-2.98)
Family hist. GBC, No	583	41	2420.07	16.94	Ref
Yes	10	0	43.89	0.0	-

Opportunistic controls: participants who attended the MAUCO clinic for other reasons and were offered an ultrasound examination. Abbreviations: GBD, gallbladder disease; p-y, person years; HR, hazard ratio; CI, confidence intervals; GBC, gallbladder cancer. a Hazard ratio from Multiple Cox extended regression.

Supplementary Table S7. Waist Circumference and Incident GSD in MAUCO 2015-2023. Cox extended *MRM.

	Hazard Ratio (95% CI) Per cm above ideal ¹
Overall	
Waist circumference, cm	1.02 (1.005-1.03)
Women	
Waist circumference, cm	1.02 (1.006-1.04)
Men	
Waist circumference, cm	1.01 (0.99-1.04)

*MRM: Multiple regression model; ¹: 80 cm for women and 94 cm for men.

Overall was adjusted by: Sex, Schooling, Family history of GBC, HDL cholesterol. Diet, Age as well as Age*Sex interaction.

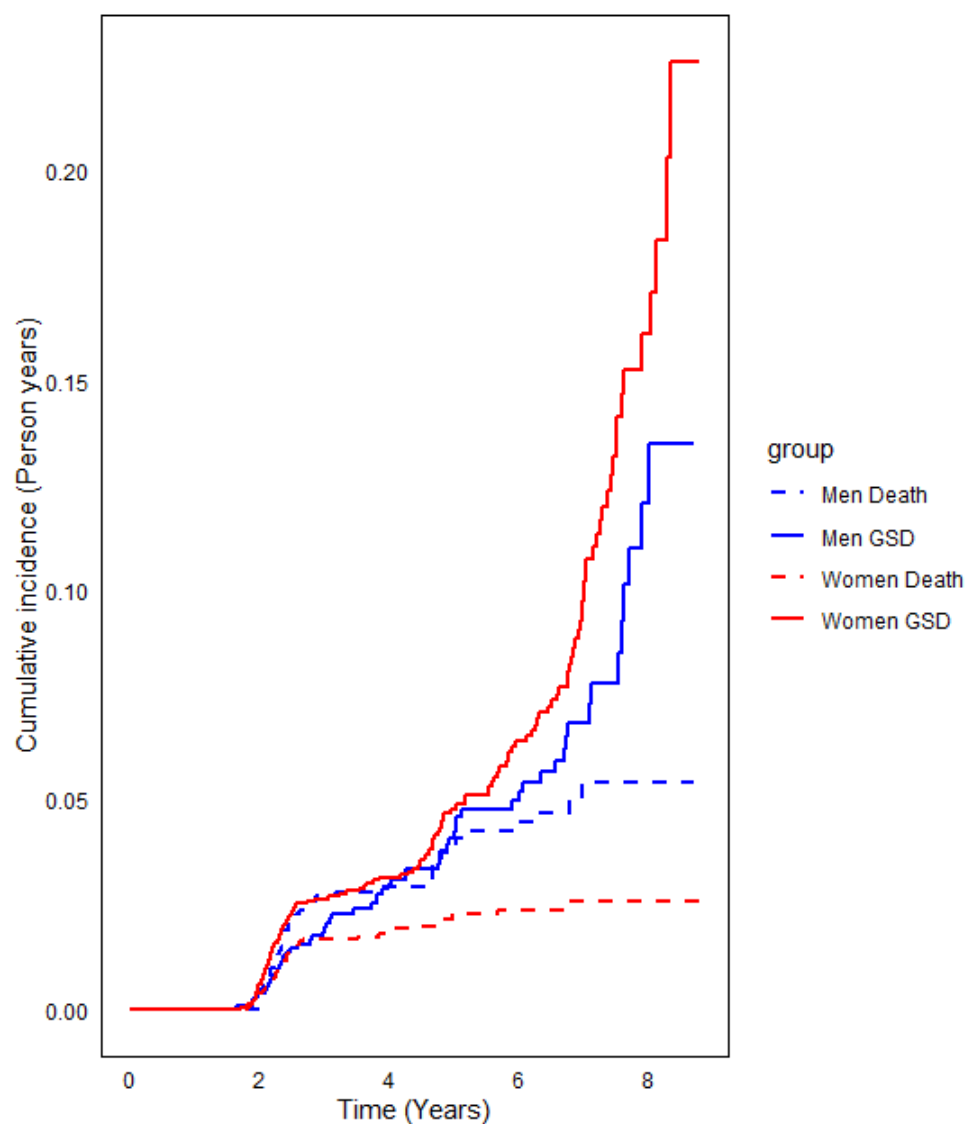
Women was adjusted as per overall model but additionally for n° of children.

Men was adjusted as per overall.

Table S8. Predictors of incident GSD (n=198) among 2284 participants. MAUCO 2019-2023.

	HR (95% CI)
Waist circumference	1.02 (1.005-1.03)
Age	1.07 (1.04-1.10)
Women (Men)	1.15 (0.79-1.67)
Schooling <4 years (≥13)	0.69 (0.33-1.43)
4-8 (≥13)	0.94 (0.56-1.57)
9-12	0.88 (0.53-1.46)
Diet med score	0.98 (0.89-1.68)
Family history GBC	1.86 (0.82-4.22)
HDL cholesterol <50 W <40m	1.22 (0.88-1.68)
Sex*Age	0.95 (0.92-0.98)

Abbreviations: GBD, gallbladder disease; p-y, person years; HR, hazard ratio; CI, confidence intervals; GBC, gallbladder cancer. a Hazard ratio from Multiple Cox extended Regression, all variables included in the model.



Supplementary Figure S3. Cumulative incidence (person-years) of GSD and Death from all-causes by follow-up years and sex.