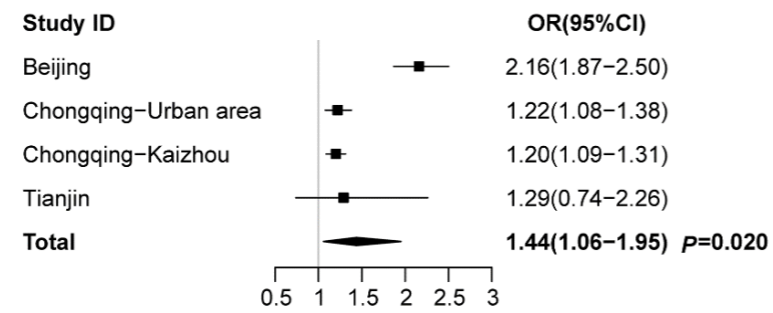


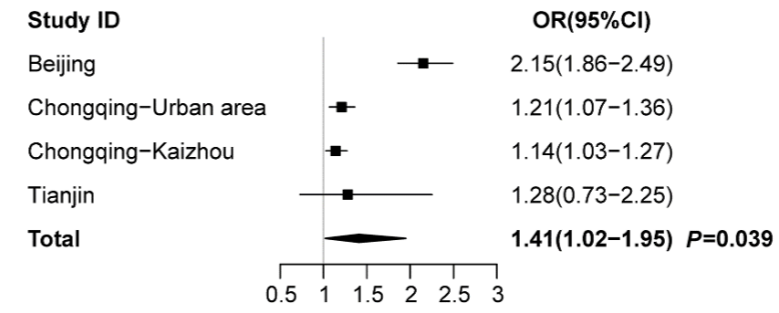
Supplementary Appendix

Supplementary Figure 1. Multivariable logistic regression analyses of the relationships among GSD subtype, KSD, and NAFLD

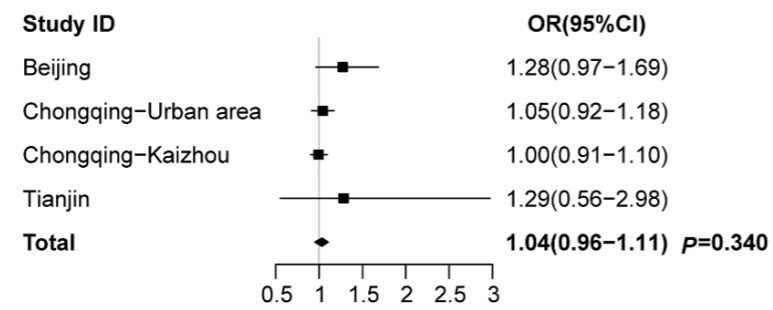
KSD-Gallstones



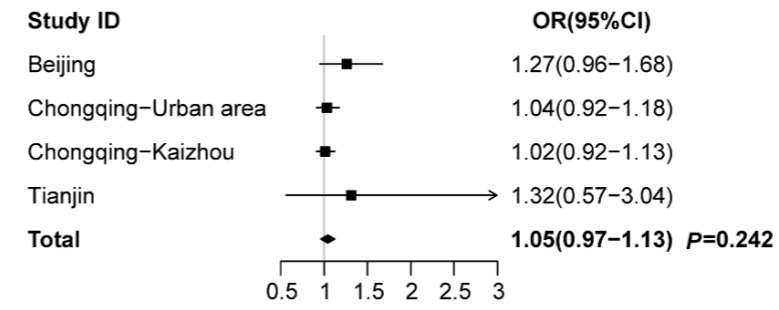
Gallstones-KSD



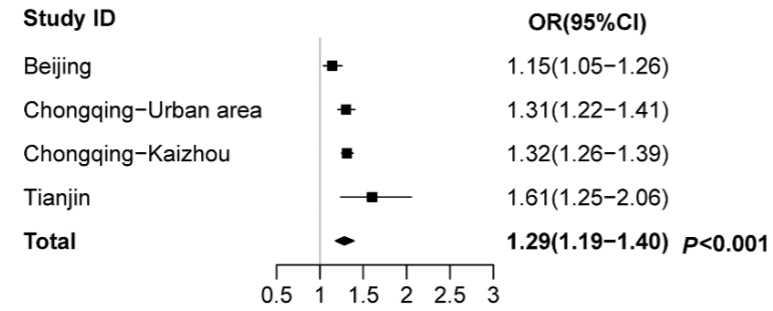
KSD-Cholecystectomy



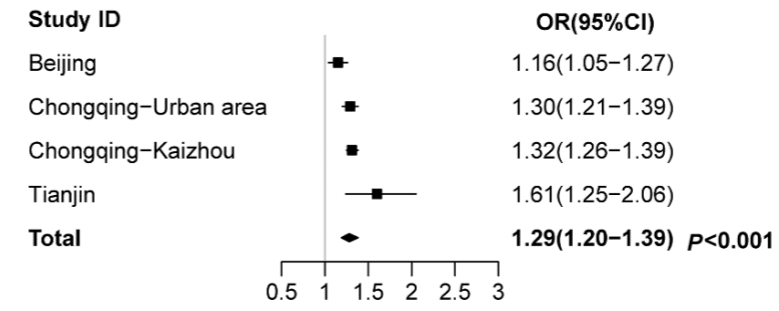
Cholecystectomy-KSD



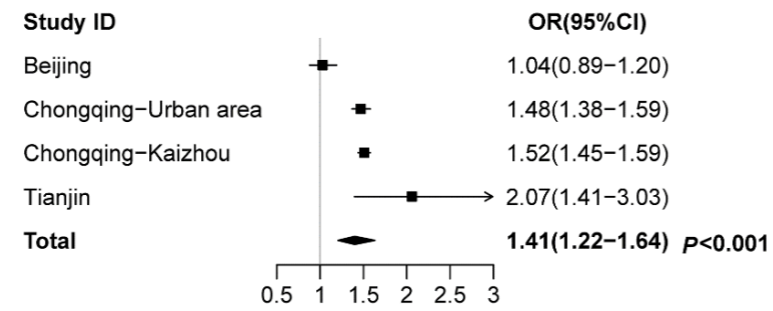
Gallstones-NAFLD



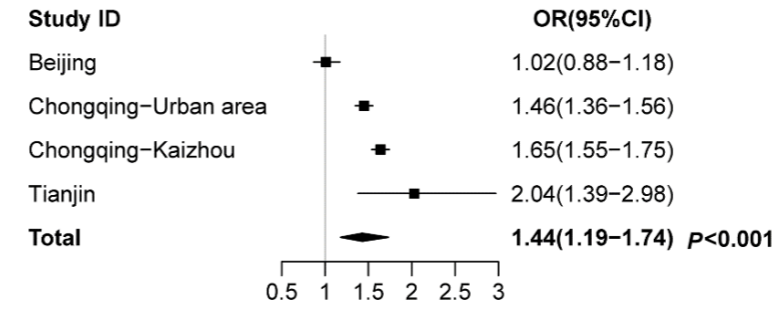
NAFLD-Gallstones



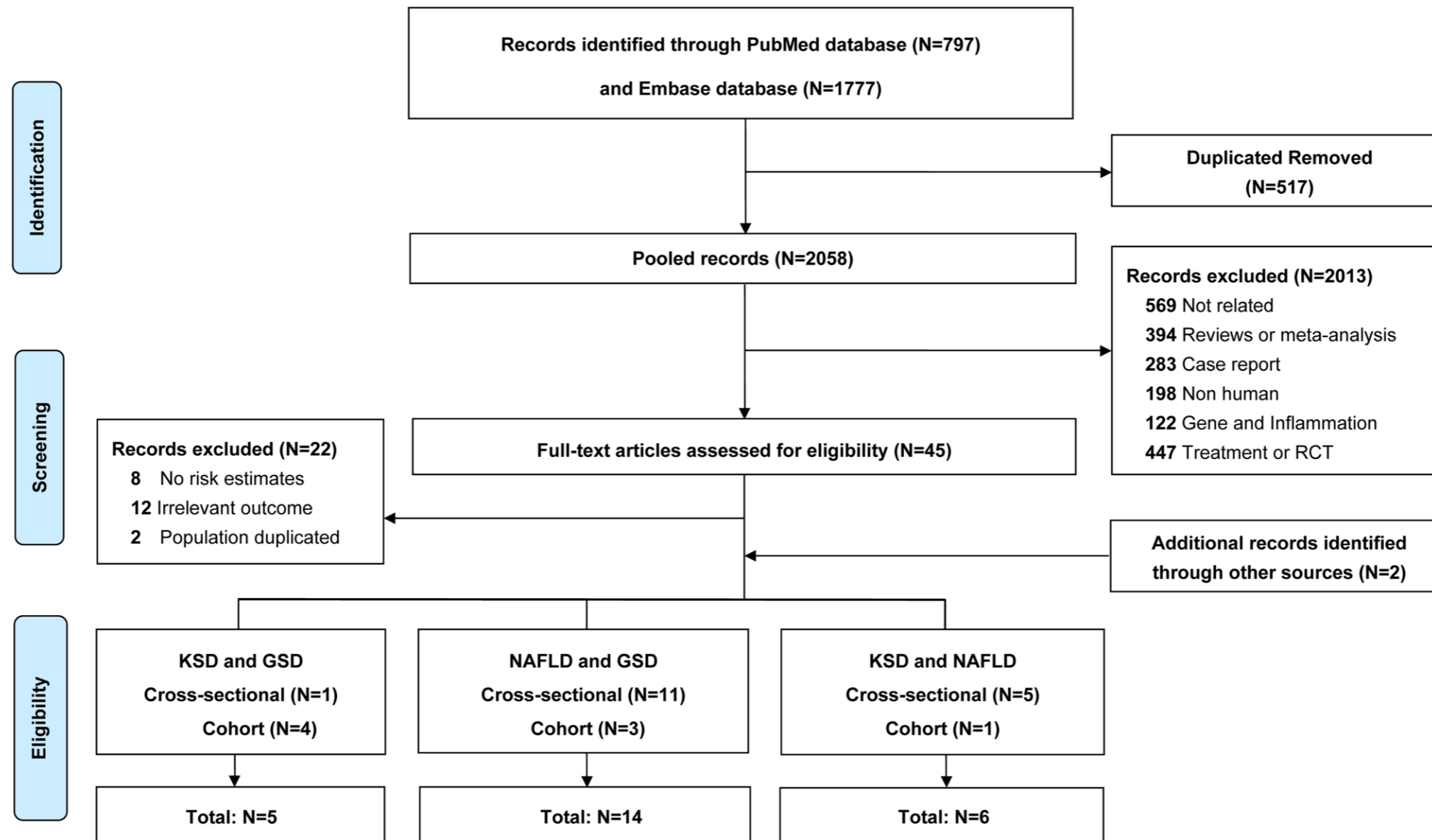
Cholecystectomy-NAFLD



NAFLD-Cholecystectomy

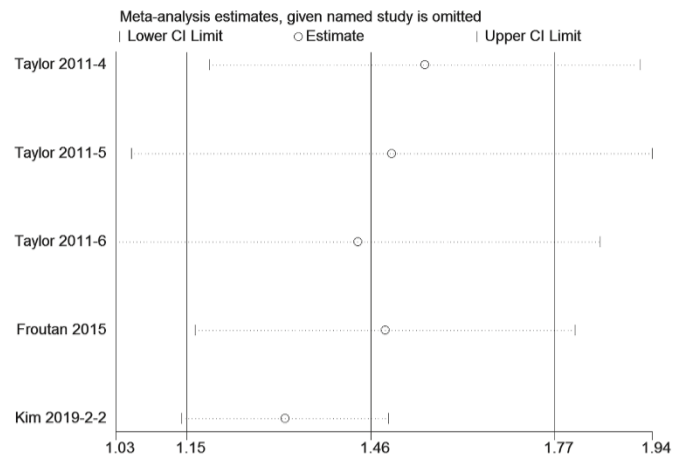


Supplementary Figure 2. Flow chart of the study selection

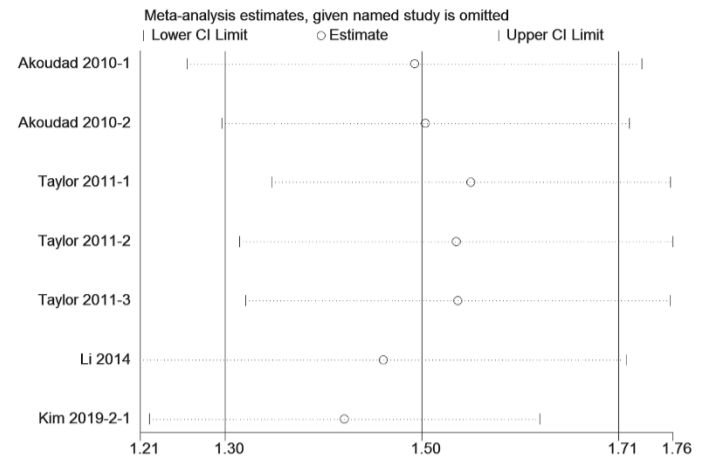


Supplementary Figure 3. Sensitivity analyses by sequentially omitting each single study from the meta-analysis

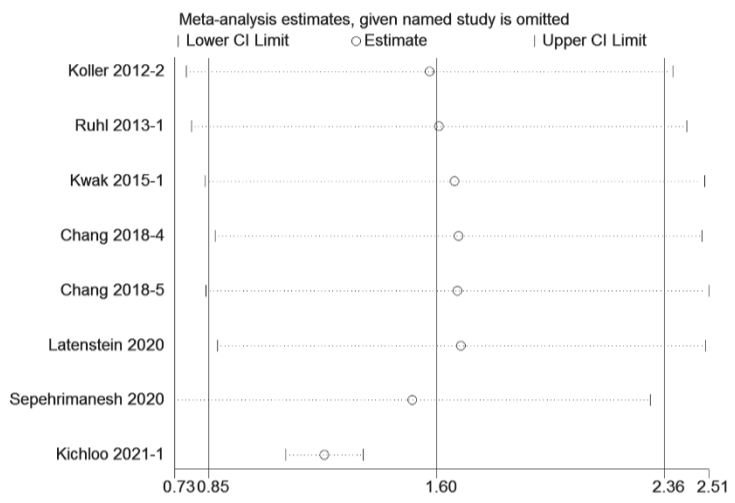
KSD-GSD



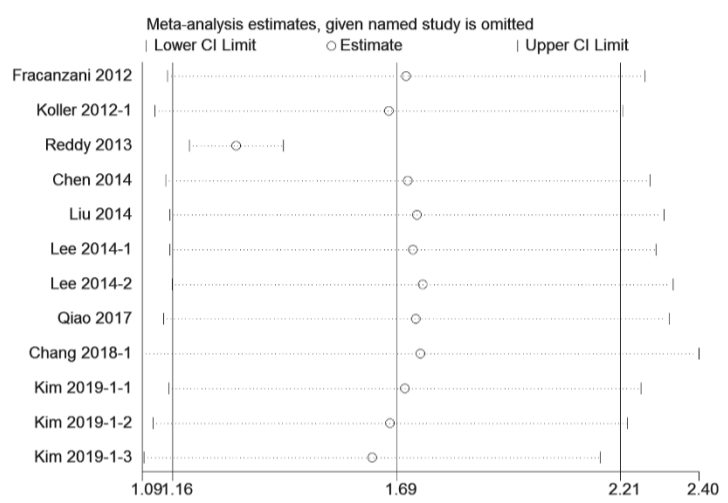
GSD-KSD



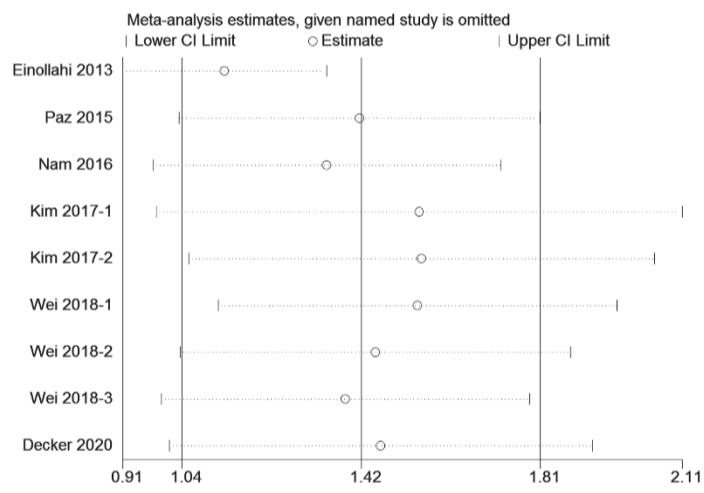
GSD-NAFLD



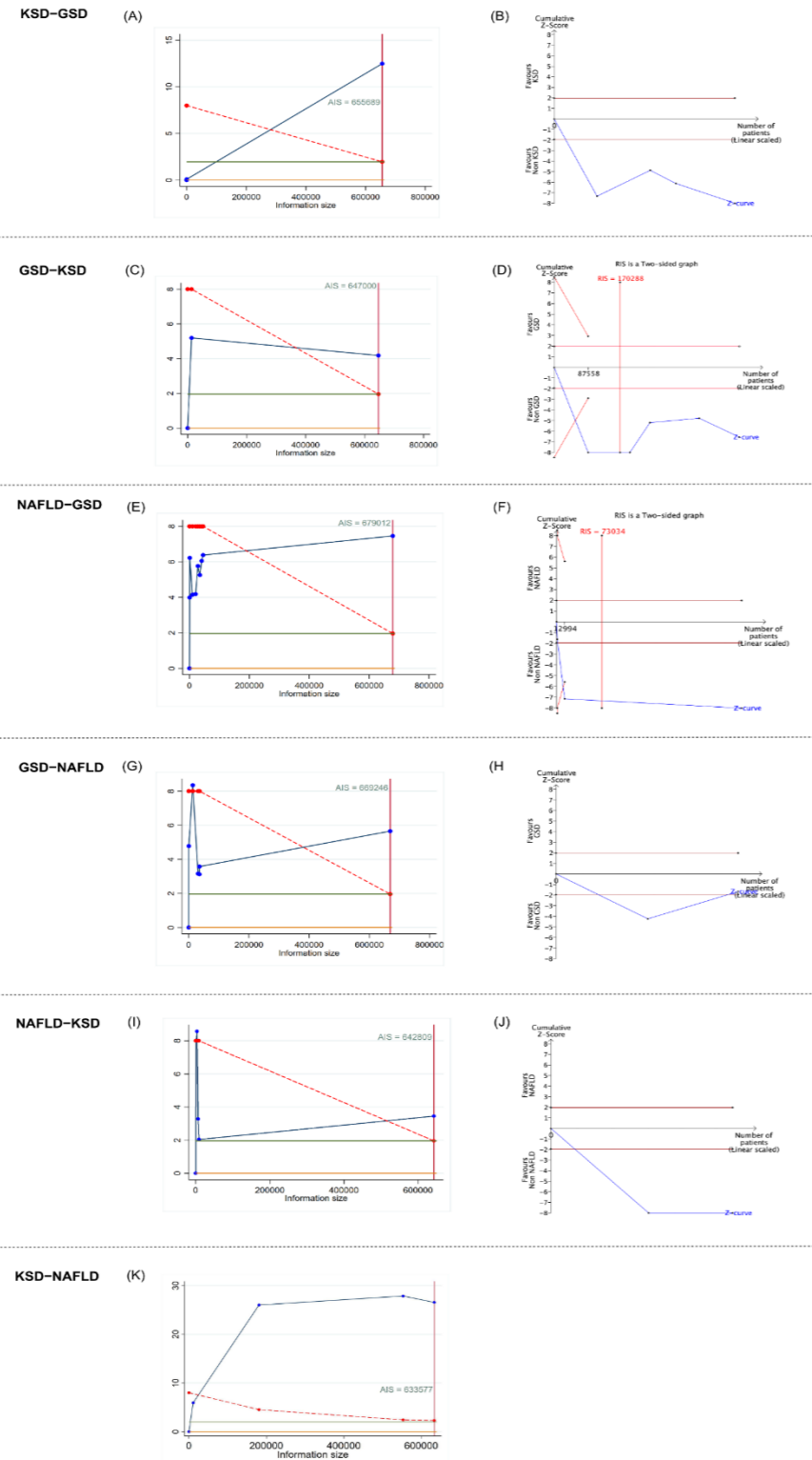
NAFLD-GSD



NAFLD-KSD



Supplementary Figure 4. Trial sequential analysis of pooled results for observational studies. The trial sequential analysis for cross-sectional studies: (A), (C), (E), (G), (I), (K). The trial sequential analysis for cohort studies: (B), (D), (F), (H), (J).



Supplementary Table 1. Search strategies

Databases	Search terms
Pubmed	<p>1. (((("kidney stone") OR "renal stones") OR nephrolithiasis) OR "calculus of kidney") OR "renal calculus") OR urolithiasis) AND (((("gallstone disease") OR gallstones) OR cholelithiasis) OR cholecystolithiasis) OR cholecystectomy)</p> <p>2. (((("kidney stone") OR "renal stones") OR nephrolithiasis) OR "calculus of kidney") OR "renal calculus") OR Urolithiasis) AND (((("Fatty Liver Disease") OR "Non-alcoholic Fatty Liver") OR NAFLD) OR NASH) OR "Nonalcoholic Steatohepatitis")</p> <p>3. (((("gallstone disease") OR gallstones) OR cholelithiasis) OR cholecystolithiasis) OR cholecystectomy) AND (((("Fatty Liver Disease") OR "Non-alcoholic Fatty Liver Disease") OR NAFLD) OR NASH) OR "Non-alcoholic Steatohepatitis")</p> <p>4. (((("Fatty Liver Disease") OR "Non-alcoholic Fatty Liver Disease") OR NAFLD) OR NASH) OR "Nonalcoholic Steatohepatitis") AND (((("gallstone disease") OR gallstones) OR cholelithiasis) OR cholecystolithiasis) OR cholecystectomy) AND (((("kidney stone") OR "renal stones") OR nephrolithiasis) OR "calculus of kidney") OR "renal calculus") OR urolithiasis)</p>
Embase	<p>'kidney stone' OR 'renal stones' OR 'nephrolithiasis' OR 'calculus of kidney' OR 'renal calculus' OR 'urolithiasis'</p> <p>#1 'gallstone disease' OR 'gallstones' OR 'cholelithiasis' OR 'cholecystolithiasis' OR</p> <p>#2 'cholecystectomy'</p> <p>'fatty liver disease' OR 'non-alcoholic fatty liver' OR 'nafld' OR 'nash' OR</p> <p>#3 'nonalcoholic steatohepatitis'</p> <p>#4 #1 AND #2</p> <p>#5 #2 AND #3</p> <p>#6 #1 AND #3</p> <p>#7 #1 AND #2 AND #3</p> <p>#8 #4 OR #5 OR #6 OR #7</p>

Supplementary Table 2. Characteristics of eligible studies

Study_ID	PMID	Author	Year	Country/Region	Study design	Period	Diagnosis-NAFLD	Diagnosis-GSD	Diagnosis-KSD	Sample size	Mean age	Follow-up	Adjustment	Risk estimates (95%CI)	NOTE
Fracanzani 2012	22848440	Fracanzani	2012	Europe	Cross-sectional study	2003-2010	Liver biopsies	ultrasound	NA	524	NA	NA	Female gender, prediabetes/diabetes, abdominal obesity, metabolic syndrome, older age, as well as higher BMI, fasting glucose, HOMAIR, higher AST/ALT ratio and lower ALT	1.46(1.08-1.99)	NAFLD→GSD
Koller 2012-1	22182015	Koller	2012	Europe	Cross-sectional study	NA	ultrasound	ultrasound	NA	482	60.77 (59.41-62.13)	NA	Age, BMI, TC, TG	1.92(1.24-2.96)	NAFLD→GSD
Koller 2012-2	22182015	Koller	2012	Europe	Cross-sectional study	NA	ultrasound	ultrasound	NA	482	60.77 (59.41-62.14)	NA	Type 2 diabetes, BMI, TG, Hypertension	1.78(1.16-2.73)	GSD→NAFLD
Reddy 2013	24363521	Reddy	2013	America	Cross-sectional study	2010	ICD-9	ICD-10	NA	303,396	NA	NA	Diabetes mellitus, hypertension, obesity, and dyslipidemia	3.59(3.40-3.79)	NAFLD→GSD
Ruhl 2013-1	23545713	Ruhl	2013	America	Cross-sectional study	1988-1994	ultrasound	ultrasound	NA	12,232	NA	NA	Age, sex, race-ethnicity, education, BMI, waist circumference, doctor-diagnosed diabetes or hemoglobin A 1C≥6.5 %, HDL cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking, alcohol intake, coffee intake, physical activity, and right upper quadrant or epigastric pain.	1.56(1.27-1.91)	GSD→NAFLD

Ruhl 2013-2	23545713	Ruhl	2013	America	Cross-sectional study	1988-1994	ultrasound	ultrasound	NA	11,437	NA	NA	Age, sex, race-ethnicity, education, BMI, waist circumference, doctor-diagnosed diabetes or hemoglobin A 1C \geq 6.5 %, HDL cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking, alcohol intake, coffee intake, physical activity, and right upper quadrant or epigastric pain.	1.09(0.84-1.42)	Gallstones \rightarrow NAFLD
Ruhl 2013-3	23545713	Ruhl	2013	America	Cross-sectional study	1988-1994	ultrasound	ultrasound	NA	11,212	NA	NA	Age, sex, race-ethnicity, education, BMI, waist circumference, doctor-diagnosed diabetes or hemoglobin A 1C \geq 6.5 %, HDL cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking, alcohol intake, coffee intake, physical activity, and right upper quadrant or epigastric pain.	2.43(1.81-3.28)	Cholecystectomy \rightarrow NAFLD
Chen 2014	24775330	Chen	2014	Chinese	Cohort study	2002-2007	ultrasound	ultrasound	NA	1,296	NA	3.51 \pm 0.84	Age, FPG, SBP, BMI, ALT	1.44(1.21-1.90)	NAFLD \rightarrow GSD
Liu 2014	25496394	Liu	2014	Chinese	Cohort study	2005-2010	ultrasound	ultrasound	NA	11,200	NA	6 years (12.73 per 1000 person-years)	Age, BMI, SBP, GLO, ALB, GLU, TG and WBC	1.24(1.00-1.53)	NAFLD \rightarrow Gallstones
Lee 2014-1	24989169	Lee	2014	Chinese	Cross-sectional study	2000-2009	ultrasound	ultrasound	NA	12,033	NA	NA	Age, gender, and BMI smoking, alcohol drinking, and regular exercise diabetes mellitus, hypertension, eGFR <60 ml/min/1.73 m ² , total cholesterol level (per	1.32(1.04-1.69)	NAFLD \rightarrow GSD

													10 mg/dl), triglyceride level (per 10 mg/dl), and HDL-C level (per 10 mg/dl)		
Lee 2014-2	24989169	Lee	2014	Chinese	Cross-sectional study	2000-2009	ultrasound	ultrasound	NA	12,033	NA	NA	Age, gender, and BMI smoking, alcohol drinking, and regular exercise diabetes mellitus, hypertension, eGFR <60 ml/min/1.73 m ² , total cholesterol level (per 10 mg/dl), triglyceride level (per 10 mg/dl), and HDL-C level (per 10 mg/dl)	1.12(0.91-1.36)	NAFLD→GSD
Kwak 2015-1	26034364	Kwak	2015	Korea	Cross-sectional study	NA	ultrasound	ultrasound	NA	17,612	48.5 years	NA	Age, sex, hypertension, diabetes, body mass index, smoking, physical activity, total cholesterol, triglycerides and HDL cholesterol.	1.22(1.04-1.43)	GSD→NAFLD
Kwak 2015-2	26034364	Kwak	2015	Korea	Cross-sectional study	NA	ultrasound	ultrasound	NA	17,612	48.5 years	NA	Age, sex, hypertension, diabetes, body mass index, smoking, physical activity, total cholesterol, triglycerides and HDL cholesterol.	1.15(0.95-1.39)	Cholecystectomy→NAFLD
Kwak 2015-3	26034364	Kwak	2015	Korea	Cross-sectional study	NA	ultrasound	ultrasound	NA	17,612	48.5 years	NA	Age, sex, hypertension, diabetes, body mass index, smoking, physical activity, total cholesterol, triglycerides and HDL cholesterol.	1.35(1.03-1.77)	Gallstones→NAFLD
Qiao 2017	28930823	Qiao	2017	Chinese	Cross-sectional study	2009-2011	ultrasound	ultrasound	NA	7,583	NA	NA	Age, sex, BMI, hyperlipidemia, raised FPG, hypertension	1.28(1.07-1.52)	NAFLD→Gallstones

Chang 2018-1	30469392	Chang	2018	Korea	Cohort study	2002-2017	ultrasound (US)	ultrasound	NA	283,446	NA	5.0 (2.4-8.9)	Age, sex, BMI, center, year of examination, education level, smoking, alcohol intake, exercise, total calorie intake, history of hypertension, history of diabetes and medication for dyslipidemia, LDL-C, HDL-C, triglycerides, HOMA-IR, or hsCRP	1.24(1.16-1.33)	NAFLD→GSD
Chang 2018-2	30469392	Chang	2018	Korea	Cohort study	2002-2017	ultrasound (US)	ultrasound	NA	283,446	NA	5.0 (2.4-8.9)	Age, sex, BMI, center, year of examination, education level, smoking, alcohol intake, exercise, total calorie intake, history of hypertension, history of diabetes and medication for dyslipidemia, LDL-C, HDL-C, triglycerides, HOMA-IR, or hsCRP	1.26(1.17-1.35)	NAFLD→Gallstones
Chang 2018-3	30469392	Chang	2018	Korea	Cohort study	2002-2017	ultrasound (US)	ultrasound	NA	283,446	NA	5.0 (2.4-8.9)	Age, sex, BMI, center, year of examination, education level, smoking, alcohol intake, exercise, total calorie intake, history of hypertension, history of diabetes and medication for dyslipidemia, LDL-C, HDL-C, triglycerides, HOMA-IR, or hsCRP	1.10(0.96-1.26)	NAFLD→Cholecystectomy
Chang 2018-4	30469392	Chang	2018	Korea	Cohort study	2002-2017	ultrasound (US)	ultrasound	NA	219,641	NA	5.0 (2.4-8.9)	Age, sex, BMI, center, year of examination, education level, smoking, alcohol intake, exercise, total calorie intake, history of hypertension, history of diabetes and medication for dyslipidemia, LDL-C, HDL-C, triglycerides, HOMA-IR, or hsCRP	1.14(1.07-1.22)	Gallstone→NAFLD

Chang 2018-5	30469392	Chang	2018	Korea	Cohort study	2002-2017	ultrasound (US)	ultrasound	NA	219,641	NA	5.0 (2.4-8.9)	Age, sex, BMI, center, year of examination, education level, smoking, alcohol intake, exercise, total calorie intake, history of hypertension, history of diabetes and medication for dyslipidemia, LDL-C, HDL-C, triglycerides, HOMA-IR, or hsCRP	1.17(1.03-1.33)	Cholecystectomy→NAFLD
Kim 2019-1-1	31277096	Kim	2019	Korea	Cross-sectional study	2009-2017	ultrasound	ultrasound	NA	7,886	NA	NA	Sex, age, and medication intake for dyslipidemia	1.48(0.88-2.09)	NAFLD→Gallstones
Kim 2019-1-2	31277096	Kim	2019	Korea	Cross-sectional study	2009-2018	ultrasound	ultrasound	NA	7,886	NA	NA	Sex, age, and medication intake for dyslipidemia	1.86(1.41-2.46)	NAFLD→Gallstones
Kim 2019-1-3	31277096	Kim	2019	Korea	Cross-sectional study	2009-2019	ultrasound	ultrasound	NA	7,886	NA	NA	Sex, age, and medication intake for dyslipidemia	3.11(1.67-5.77)	NAFLD→Gallstones
Latenstein 2020	32352682	Latenstein	2020	the Netherlands	Cross-sectional study	2009-2011,2012-2014	ultrasound	Questionair+ Medical record	NA	4,307	66.0±8	NA	Age, sex, education, physical activity, energy intake, hypertension, diabetes, metabolic syndrome, BMI	1.04(0.62-1.77)	Cholecystectomy→NAFLD
Kichloo 2021-1	NA	Kichloo	2021	America	Cross-sectional study	2016-2017	ICD-10	ICD-10	NA	14,294,784	NA	NA	Age, gender, race, alcohol abuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, nicotine dependence, and obesity	2.75(2.70-2.79)	GSD→NAFLD
Kichloo 2021-2	NA	Kichloo	2021	America	Cross-sectional study	2016-2017	ICD-10	ICD-10	NA	NA	NA	NA	Age, gender, race, alcohol abuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, nicotine dependence, and obesity	6.32(6.15-6.48)	Gallstones→NAFLD

Kichloo 2021-3	NA	Kichloo	2021	America	Cross-sectional study	2016-2017	ICD-10	ICD-10	NA	NA	NA	NA	Age, gender, race, alcohol abuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, nicotine dependence, and obesity	1.97(1.93-2.01)	Cholecystectomy→NAFLD
Sepehrimaneh 2020	32431528	Sepehrimaneh	2020	Iran	Cross-sectional study	2012-2019	ultrasound	ultrasound	NA	236	NA	NA	NA	2.52(1.35-4.71)	GSD→NAFLD
Einollahi 2013	23363254	Einollahi	2013	Iran	Cross-sectional study	NA	ultrasound	NA	ultrasound	11,245	NA	NA	NA	2.40(2.10-2.70)	NAFLD → KSD
Paz 2015	NA	Paz	2015	European	Cross-sectional study	NA	CT	NA	CT	100	49.80	NA	NA	5.40(1.17-24.92)	NAFLD → KSD
Nam 2016	27536709	Nam	2016	Korea	Cross-sectional study	2015	CT	NA	CT	1,381	NA	NA	Gender, Age, Hounsfield Unit	5.00(3.00-8.20)	NAFLD → KSD
Kim 2017-1	29073130	Kim	2017	Korea	Cohort study	2002-2015	ultrasound	NA	ultrasound	208,578	NA	6.6 (3.0-9.4) 1,054,887.7 person-year	Adjusted for age, center, year of screening exam, smoking status, alcohol intake, physical activity, education level, BMI, and history of hypertension and diabetes, HOMA-IR, uric acid, and hsCRP BMI, body mass index	1.17(1.06-1.30)	NAFLD → KSD
Kim 2017-2	29073130	Kim	2017	Korea	Cohort study	2002-2015	ultrasound	NA	ultrasound	208,578	NA	6.6 (3.0-9.4) 1,054,887.8 person-year	Adjusted for age, center, year of screening exam, smoking status, alcohol intake, physical activity, education level, BMI, and history of hypertension and diabetes, HOMA-IR, uric acid, and hsCRP BMI, body mass index	0.97(0.81-1.16)	NAFLD → KSD

Wei 2018-1	29507274	Wei	2018	Chinese	Cross-sectional study	NA	ultrasound	NA	ultrasound	3,179	17-88 Years	NA	Age, education status, smoking, alcohol consumption, and physical activity, BMI	0.78(0.51-1.21)	NAFLD → KSD
Wei 2018-2	29507274	Wei	2018	Chinese	Cross-sectional study	NA	ultrasound	NA	ultrasound	3,179	17-88 Years	NA	Age, education status, smoking, alcohol consumption, and physical activity, BMI	1.23(0.75-2.03)	NAFLD → KSD
Wei 2018-3	29507274	Wei	2018	Chinese	Cross-sectional study	NA	ultrasound	NA	ultrasound	3,179	17-88 Years	NA	Age, education status, smoking, alcohol consumption, and physical activity, BMI	2.11(1.08-4.14)	NAFLD → KSD
Decker 2020	32571100	Decker	2020	America	Cross-sectional study	1988-1994	ultrasound	NA	ultrasound	11,859	NA	NA	Age, sex, race, BMI, smoking status, liver enzyme level, and diagnoses of metabolic comorbidities	1.29(1.01-1.61)	NAFLD → KSD
Akoudad 2010-1	20801154	Akoudad	2010	America	Cohort study	1993-1995	NA	Questionair	ICD-9 codes	11,173	NA	10.8 years	Age, gender, race, region, waist circumference, triglycerides, hypertension, diabetes, uric acid	1.41(0.78-2.55)	GSD → KSD
Akoudad 2010-2	20801154	Akoudad	2010	America	Cross-sectional study	1993-1995	NA	Questionair	Questionair	12,161	NA	NA	Age, gender, race, region, waist circumference, triglycerides, hypertension, diabetes, uric acid and	1.54(1.31-1.81)	GSD → KSD
Taylor 2011-1	21944091	Taylor	2011	America	Cohort study (NHS I)	1980-2004	NA	Questionair	Questionair	95,537	NA	24 years	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use , family history of kidney stones, history of hypertension, history of diabetes , calcium supplement use, and dietary intake of calcium, animal protein, potassium,	1.26(1.09-1.44)	Cholecystectomy→KSD

													sodium, magnesium, sucrose, and caffeine .		
Taylor 2011-2	21944091	Taylor	2011	America	Cohort study (NHS II)	1991-2005	NA	Questionair	Questionair	101,587	NA	14 years	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use , family history of kidney stones, history of hypertension, history of diabetes , calcium supplement use, and dietary intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine .	1.32(1.14-1.52)	GSD → KSD
Taylor 2011-3	21944091	Taylor	2011	America	Cohort study (HPFS)	1986-2004	NA	Questionair	Questionair	45,794	NA	18 years	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use , family history of kidney stones, history of hypertension, history of diabetes , calcium supplement use, and dietary intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine .	1.28(1.03-1.57)	GSD → KSD
Taylor 2011-4	21944091	Taylor	2011	America	Cohort study (NHS I)	1980-2004	NA	Questionair	Questionair	97,185	NA	24 years	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use, history of hypertension, history of diabetes, calcium supplement use, and intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine.	1.17(1.06-1.29)	KSD → Cholecystectomy

Taylor 2011-5	21944091	Taylor	2011	America	Cohort study (NHS II)	1991-2005	NA	Questionair	Questionair	99,605	NA	14 years	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use, history of hypertension, history of diabetes, calcium supplement use, and intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine.	1.31(1.19-1.45)	KSD → GSD
Taylor 2011-6	21944091	Taylor	2011	America	Cohort study (HPFS)	1986-2004	NA	Questionair	Questionair	48,900	NA	18 years	Age, body mass index, use of thiazide diuretics, fluid intake, alcohol use, history of hypertension, history of diabetes, calcium supplement use, and intake of calcium, animal protein, potassium, sodium, magnesium, sucrose, and caffeine.	1.51(1.35-1.68)	KSD → GSD
Li 2014	24453284	Li	2014	Chinese	Cohort study	1996-2010	NA	ICD-9-CM	ICD-9-CM	126,287	NA	15 years	age, sex and comorbidities.	1.68(1.59-1.77)	Gallstones-KSD
Froutan 2015	26379936	Froutan	2015	Iran	Cross-sectional study	2012-2014	NA	ultrasound	ultrasound	195	48 ± 11.4	NA	NA	0.94(0.30-2.97)	KSD → Gallstones
Kim 2019-2-1	30796254	Kim	2019	Korea	Cohort study I	2002-2013	NA	ICD-10	ICD-10	103,555	NA	65.74 ± 41.60	Age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.	1.93(1.75-2.14)	Gallstones-KSD
Kim 2019-2-2	30796254	Kim	2019	Korea	Cohort study II	2002-2013	NA	ICD-10	ICD-10	118,075	NA	72.25 ± 41.52	Age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.	1.97(1.81-2.15)	KSD → Gallstones

Supplementary Table 3. Assessment of quality of included cohort studies (The Newcastle-Ottawa Quality Assessment Scale (NOS))

Study	Selection	Comparability	Outcome	Total
Akoudad 2010	★★★★	★	★★	7
Taylor 2011	★★★	★★	★★	7
Chen 2014	★★★	★	★★	6
Li 2014	★★★★	★	★★	7
Liu 2014	★★★★	★★	★★	8
Kim 2017	★★★★	★★	★★	8
Chang 2018	★★★★	★★	★★	8
Kim 2019-2	★★★★	★	★★★	8

Supplementary Table 4. Assessment of quality of included cross-sectional study (Agency for Healthcare Research and Quality (AHRQ))

Authors (References)	Akoudad 2010	Fracanzani 2012	Koller 2012	Einollahi 2013	Reddy 2013	Ruhl 2013	Lee 2014	Froutan 2015	Kwak 2015	Paz 2015	Nam 2016	Qiao 2017	Wei 2018	Kim 2019-1	Decker 2020	Latenstein 2020	Sepehrimanesh 2020	Kichloo 2021
1) Define the source of information (survey, record review)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3) Indicate time period used for identifying patients	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1
4) Indicate whether or not subjects were consecutive if not population-based	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7) Explain any patient exclusions from analysis	1	1	1	0	1	1	0	0	1	0	1	1	0	1	0	1	1	0
8) Describe how confounding was assessed and/or controlled.	1	1	1	0	1	1	1	0	1	0	1	1	1	1	1	1	0	1
9) If applicable, explain how missing data were handled in the analysis	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
10) Summarize patient response rates and completeness of data collection	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	7	6	5	2	7	7	5	4	6	2	6	6	5	6	5	6	5	5