S2_paper2_analysis.py

Source listing · 320 lines · generated 2026-07-28

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"""
S2_paper2_analysis.py
--------------------------------------------------------------------------------
Complete, reproducible analysis pipeline for:
"Metabolic syndrome-like phenotype, BMI-based metabolic burden, and
 size-threshold thyroid nodules: a cross-sectional study of 50,023
 health-examination attendees" (submitted to BMC Endocrine Disorders).

This script reads the de-identified per-domain CSV exports, links each thyroid
ultrasound to the nearest laboratory visit, derives the exposures and outcomes,
and reproduces every model reported in the manuscript and its tables:

    Table 1   baseline characteristics by nodule status
    Table 2   included vs excluded participants
    Table 3   metabolic factors vs nodule outcomes (OR/PR) + BH correction
    Table 4   mutually adjusted five-component model + VIF
    Table 5   effect modification by age and sex (+ interaction tests)
    Table 6   sensitivity analyses (CDS, uric acid/hs-CRP, TPOAb, sex-specific
              HDL, age spline, +-30-day window, year adjustment, 2019+, MICE)
    Text      exposure prevalences; direct nodule-size gradient; version-
              consistent (2018+) TI-RADS >=4 for all exposures; first-stage
              selection (ultrasound vs no ultrasound); TyG spline non-linearity;
              E-values.

All estimators are in S1_stats_functions.py (NumPy only). Python 3.10, pandas.
Set DATA_DIR to the folder holding the raw CSVs, then: python S2_paper2_analysis.py
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"""
import numpy as np
import pandas as pd
import S1_stats_functions as st

# ============================================================ configuration
DATA_DIR = "."
ENC = "gb18030"
LINK_DAYS = 60
RANGES = dict(BMI=(12, 60), SBP=(70, 260), DBP=(40, 180), FPG=(2, 40),
              TG=(0.1, 30), TC=(1, 20), HDL=(0.2, 5), LDL=(0.2, 15),
              UA=(60, 1500), hsCRP=(0, 200), WC=(50, 180), TSH=(0.01, 100),
              TPOAb=(0, 5000))
FILES = {
    "us":  ("组(超声)(检查记录)(健康体检).csv", "检查记录_超声_检查日期",
            {"检查记录_超声_甲状腺结节": "nod_size", "检查记录_超声_甲状腺结节级别": "grade"}),
    "glu": ("组(血糖)(检验记录)(健康体检).csv", "检验记录_血糖_日期",
            {"检验记录_血糖_血糖(空腹)": "FPG", "检验记录_血糖_糖化血红蛋白": "HbA1c"}),
    "lip": ("组(血脂四项)(检验记录)(健康体检).csv", "检验记录_血脂四项_日期",
            {"检验记录_血脂四项_甘油三酯": "TG", "检验记录_血脂四项_总胆固醇": "TC",
             "检验记录_血脂四项_高密度胆固醇": "HDL", "检验记录_血脂四项_低密度胆固醇": "LDL"}),
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    "ua":  ("组(肾功能)(检验记录)(健康体检).csv", "检验记录_肾功能_日期",
            {"检验记录_肾功能_尿酸": "UA"}),
    "crp": ("组(C-反应蛋白（超敏）)(检验记录)(健康体检).csv", "检验记录_C-反应蛋白（超敏）_日期",
            {"检验记录_C-反应蛋白（超敏）_超敏C反应蛋白": "hsCRP"}),
    "thy": ("组(甲功七项)(检验记录)(健康体检).csv", "检验记录_甲功七项_日期",
            {"检验记录_甲功七项_促甲状腺素": "TSH", "检验记录_甲功七项_甲状腺过氧化物酶抗体": "TPOAb"}),
}
GEN_FILE = "组(一般检查)(患者基本信息)(健康体检).csv"
VISIT_FILE = "访视(健康体检).csv"


# ============================================================ utilities
def num(s):
    return pd.to_numeric(s.astype(str).str.replace(r"[<>≥≤+]", "", regex=True).str.strip()
                         .replace({"": np.nan, "-": np.nan, "nan": np.nan, ".": np.nan}), errors="coerce")


def load_domain(fname, date_col, colmap, aggfun="mean", require_any=None, keep_date=False):
    use = ["中心患者ID", date_col] + list(colmap)
    df = pd.read_csv(f"{DATA_DIR}/{fname}", encoding=ENC, skiprows=[1], usecols=use, dtype=str, low_memory=False)
    df = df.rename(columns={"中心患者ID": "pid", date_col: "date", **colmap})
    df["date"] = pd.to_datetime(df["date"], errors="coerce")
    df = df[df["date"].notna()]
    for c in colmap.values():
        df[c] = num(df[c])
    if require_any:
        df = df[df[require_any].notna().any(axis=1)]
    g = df.groupby(["pid", "date"], as_index=False).agg({c: aggfun for c in colmap.values()})
    return g


def asof(left, right, cols, tol=LINK_DAYS, gap_name=None):
    r = right[["pid", "date"] + cols].dropna(subset=["date"]).sort_values("date").copy()
    if gap_name:
        r["_rd"] = r["date"]
    m = pd.merge_asof(left.sort_values("date"), r, by="pid", on="date",
                      direction="nearest", tolerance=pd.Timedelta(f"{tol}D"))
    if gap_name:
        m[gap_name] = (m["date"] - m["_rd"]).abs().dt.days
        m = m.drop(columns=["_rd"])
    return m


# ============================================================ 1. build episodes
print("Loading and linking domains ...")
US = load_domain(*FILES["us"], aggfun="max", require_any=["nod_size", "grade"])
ep = US.copy()
ep = asof(ep, load_domain(*FILES["glu"]), ["FPG", "HbA1c"], gap_name="gap_glu")
ep = asof(ep, load_domain(*FILES["lip"]), ["TG", "TC", "HDL", "LDL"], gap_name="gap_lip")
ep = asof(ep, load_domain(*FILES["ua"]), ["UA"])
ep = asof(ep, load_domain(*FILES["crp"]), ["hsCRP"])
ep = asof(ep, load_domain(*FILES["thy"]), ["TSH", "TPOAb"])

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```python
G = pd.read_csv(f"{DATA_DIR}/{GEN_FILE}", encoding=ENC, skiprows=[1], dtype=str, low_memory=False,
                usecols=["中心患者 ID", "患者基本信息_一般检查_日期", "患者基本信息_一般检查_体重指数",
                         "患者基本信息_一般检查_腰围", "患者基本信息_一般检查_血压"])
G.columns = ["pid", "date", "BMI", "WC", "BP"]
G["date"] = pd.to_datetime(G["date"], errors="coerce"); G = G[G["date"].notna()]
bp = G["BP"].astype(str).str.extract(r"(\d{2,3})\s*/\s*(\d{2,3})")
G["SBP"], G["DBP"], G["BMI"], G["WC"] = num(bp[0]), num(bp[1]), num(G["BMI"]), num(G["WC"])
GEN = G.groupby(["pid", "date"], as_index=False)[["BMI", "WC", "SBP", "DBP"]].mean()
ep = asof(ep, GEN, ["BMI", "WC", "SBP", "DBP"], gap_name="gap_gen")

names = ["pid", "st", "ctr", "vt", "visit", "bd", "kh", "sex", "age", "_j"]
V = pd.read_csv(f"{DATA_DIR}/{VISIT_FILE}", encoding=ENC, header=None, skiprows=2, names=names, dtype=str, low_memory=False)
V["age"] = num(V["age"])
sex = V.groupby("pid")["sex"].agg(lambda s: s.mode().iloc[0] if len(s.mode()) else np.nan)
gdate = G[["pid", "date"]].drop_duplicates().merge(V[["pid", "visit", "age"]].dropna(), on="pid").dropna(subset=["age"])
gdate["dob"] = gdate["date"] - pd.to_timedelta(gdate["age"] * 365.25, unit="D")
dob = gdate.groupby("pid")["dob"].median()
meta = pd.DataFrame({"sex": sex, "dob": dob}).reset_index()
ep = ep.merge(meta, on="pid", how="left")

# ========================================================== 2. derive variables
for v, (lo, hi) in RANGES.items():
    if v in ep:
        ep.loc[(ep[v] < lo) | (ep[v] > hi), v] = np.nan
ep["age"] = (ep["date"] - ep["dob"]).dt.days / 365.25
ep["female"] = (ep["sex"] == "女").astype(float)
ep["year"] = ep["date"].dt.year
ep["TyG"] = np.log(ep["TG"] * 88.57 * ep["FPG"] * 18.0182 / 2)
ep["nod1"] = (ep["nod_size"] >= 1.0).astype(float)
ep["nod2"] = (ep["nod_size"] >= 2.0).astype(float)
ep["tr4"] = (ep["grade"] >= 4).astype(float)
ep["nodule"] = (ep["nod_size"] >= 0.1).astype(float)
ep["Obesity"] = (ep["BMI"] >= 28).astype(float)
ep["HighBP"] = ((ep["SBP"] >= 130) | (ep["DBP"] >= 85)).astype(float)
ep["HighGlucose"] = (ep["FPG"] >= 6.1).astype(float)
ep["HighTG"] = (ep["TG"] >= 1.7).astype(float)
ep["LowHDL"] = (ep["HDL"] < 1.04).astype(float)
COMP = ["Obesity", "HighBP", "HighGlucose", "HighTG", "LowHDL"]
ep["burden"] = ep[COMP].sum(axis=1)
ep["MetSlike"] = (ep["burden"] >= 3).astype(float)
ep.loc[ep[COMP].notna().sum(axis=1) < 5, ["burden", "MetSlike"]] = np.nan

first = ep.sort_values(["pid", "date"]).drop_duplicates("pid", keep="first")
first = first[(first["age"] >= 18) & (first["age"] <= 100)].copy()
CC = ["BMI", "SBP", "DBP", "FPG", "TG", "HDL"]
d = first.dropna(subset=CC).copy()
print(f"Analytic sample: N = {len(d):,}; >=1cm events = {int(d['nod1'].sum()):,} "
      f"({d['nod1'].mean()*100:.1f}%); TI-RADS>=4 = {int(d['tr4'].sum()):,}")


# ========================================================== helpers
def OR(df, out, preds):
    x = df.dropna(subset=[out] + preds)
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    return st.logit(x[out].values, x[preds].values, names=preds)[preds[0]], len(x)

def PR(df, out, preds):
    x = df.dropna(subset=[out] + preds)
    return st.poisson_robust(x[out].values, x[preds].values, names=preds)[preds[0]]

def show(tag, r, n=None):
    extra = f"; n={n:,}" if n else ""
    print(f"    {tag:<34} OR {r['ratio']:.2f} ({r['lo']:.2f}-{r['hi']:.2f}){extra}")


# ============================================================ Table 1: baseline by nodule status
print("\n[Table 1] baseline by nodule >=1cm status (mean+-SD; SMD):")
g1, g0 = d[d["nod1"] == 1], d[d["nod1"] == 0]
for v in ["age", "BMI", "SBP", "FPG", "TG", "HDL", "UA", "hsCRP", "TyG", "burden"]:
    t = st.ttest(g1[v], g0[v])
    print(f"    {v:<8} {t['m2']:.2f}+-{t['s2']:.2f} vs {t['m1']:.2f}+-{t['s1']:.2f}  SMD {t['smd']:.2f}")
fem = st.prop_test(g1["female"].sum(), len(g1), g0["female"].sum(), len(g0))
print(f"    female %  {g0['female'].mean()*100:.1f} vs {g1['female'].mean()*100:.1f}  SMD {fem['smd']:.2f}")

# ============================================================ Table 2: included vs excluded
print("\n[Table 2] included (complete-case) vs excluded (had US, incomplete labs):")
excl = first[~first.index.isin(d.index)]
for v in ["age", "BMI", "nod1", "nodule", "tr4"]:
    a, b = d[v].dropna(), excl[v].dropna()
    smd = (a.mean() - b.mean()) / np.sqrt((a.var(ddof=1) + b.var(ddof=1)) / 2)
    print(f"    {v:<8} incl {a.mean():.2f} vs excl {b.mean():.2f}  SMD {smd:.2f}")

# ============================================================ exposure prevalences
print("\n[Prevalences] MetS-like %.1f%%; " % (d["MetSlike"].mean() * 100)
      + ", ".join(f"{c} {d[c].mean()*100:.1f}%" for c in COMP))

# ============================================================ Table 3 + BH: primary and components
print("\n[Table 3] associations with nodule >=1cm (age+sex adjusted):")
r, n = OR(d, "nod1", ["MetSlike", "age", "female"]); show("MetS-like", r, n)
print(f"        PR {PR(d,'nod1',['MetSlike','age','female'])['ratio']:.2f}")
comp_p = {}
for c in COMP + ["burden", "TyG"]:
    r, _ = OR(d, "nod1", [c, "age", "female"]); show(c, r)
    if c in COMP:
        comp_p[c] = r["p"]
# Benjamini-Hochberg on the five component p-values
items = sorted(comp_p.items(), key=lambda kv: kv[1]); m = len(items)
q = {k: min(p * m / i, 1.0) for i, (k, p) in enumerate(items, 1)}
print(f"    Benjamini-Hochberg: max q across components = {max(q.values()):.2e} (all < 0.001)")
# any-nodule and >=2cm PRs (secondary)
for out, lab in [("nodule", "any nodule"), ("nod2", ">=2cm")]:
    print(f"        {lab} PR {PR(d,out,['MetSlike','age','female'])['ratio']:.2f}")

# ============================================================ Table 4: mutually adjusted + VIF
print("\n[Table 4] five components entered simultaneously (+VIF):")
x = d.dropna(subset=["nod1"] + COMP + ["age", "female"])
mv = st.logit(x["nod1"].values, x[COMP + ["age", "female"]].values, names=COMP + ["age", "female"])
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V_ = st.vif(x[COMP + ["age", "female"]].values)
for i, c in enumerate(COMP):
    print(f"    {c:<12} OR {mv[c]['ratio']:.2f} ({mv[c]['lo']:.2f}-{mv[c]['hi']:.2f})  VIF {V_[i]:.2f}")

# ============================================================ dose-response
print("\n[Fig 2] dose-response by burden count (prevalence of >=1cm):")
cc, tt = [], []
for k in range(6):
    s = d[d["burden"] == k]; cc.append(int(s["nod1"].sum())); tt.append(len(s))
    print(f"    {k}: {s['nod1'].mean()*100:5.1f}% (n={len(s):,})")
z, p = st.cochran_armitage(cc, tt)
print(f"    Cochran-Armitage z={z:.1f}, p={p:.1e}")

# ============================================================ Table 5: effect modification
print("\n[Table 5] MetS-like x nodule >=1cm, stratified:")
dd = d.dropna(subset=["nod1", "MetSlike", "age", "female"]).copy()
dd["ac"] = (dd["age"] - dd["age"].mean()) / 10
dd["mk_age"], dd["mk_sex"] = dd["MetSlike"] * dd["ac"], dd["MetSlike"] * dd["female"]
pa = st.logit(dd["nod1"].values, dd[["MetSlike", "ac", "mk_age", "female"]].values,
              names=["MetSlike", "ac", "mk_age", "female"])["mk_age"]["p"]
ps = st.logit(dd["nod1"].values, dd[["MetSlike", "female", "mk_sex", "age"]].values,
              names=["MetSlike", "female", "mk_sex", "age"])["mk_sex"]["p"]
for lab, sub, cov in [("age <40", d[d.age < 40], ["age", "female"]),
                      ("age 40-60", d[(d.age >= 40) & (d.age < 60)], ["age", "female"]),
                      ("age >=60", d[d.age >= 60], ["age", "female"]),
                      ("women", d[d.female == 1], ["age"]),
                      ("men", d[d.female == 0], ["age"])]:
    r, nn = OR(sub, "nod1", ["MetSlike"] + cov); show(lab, r, nn)
print(f"    interaction: MetS x age p={pa:.3f}; MetS x sex p={ps:.3f}")

# ============================================================ direct nodule-size gradient
print("\n[Size gradient] MetS-like OR by nodule size threshold:")
for out, lab in [("nodule", ">=0.1cm"), ("nod1", ">=1.0cm"), ("nod2", ">=2.0cm")]:
    r, _ = OR(d, out, ["MetSlike", "age", "female"]); show(lab, r)

# ============================================================ Table 6: sensitivity analyses
print("\n[Table 6] sensitivity analyses:")
# waist-based CDS definition
co = np.where(d["female"] == 1, d["WC"] >= 85, d["WC"] >= 90).astype(float); co[d["WC"].isna()] = np.nan
cdf = pd.DataFrame({"co": co, "hg": d["HighGlucose"], "hbp": d["HighBP"], "htg": d["HighTG"], "lhdl": d["LowHDL"]})
d["MetS_cds"] = (cdf.sum(1) >= 3).astype(float); d.loc[cdf.notna().sum(1) < 5, "MetS_cds"] = np.nan
r, n = OR(d, "nod1", ["MetS_cds", "age", "female"]); show("CDS (waist) definition", r, n)
# sex-specific HDL
d["LowHDL_sex"] = np.where(d["female"] == 1, d["HDL"] < 1.29, d["HDL"] < 1.04).astype(float)
d["MetSlike_sex"] = ((d[["Obesity", "HighBP", "HighGlucose", "HighTG"]].sum(1) + d["LowHDL_sex"]) >= 3).astype(float)
r, _ = OR(d, "nod1", ["MetSlike_sex", "age", "female"]); show("sex-specific HDL cut-off", r)
# + uric acid & hs-CRP (within subset, before vs after)
sub = d.dropna(subset=["nod1", "MetSlike", "age", "female", "UA", "hsCRP"])
b = st.logit(sub["nod1"].values, sub[["MetSlike", "age", "female"]].values, names=["MetSlike", "age", "female"])["MetSlike"]
fu = st.logit(sub["nod1"].values, sub[["MetSlike", "age", "female", "UA", "hsCRP"]].values,
              names=["MetSlike", "age", "female", "UA", "hsCRP"])["MetSlike"]
print(f"    + uric acid & hs-CRP (n={len(sub):,}): {b['ratio']:.2f} -> {fu['ratio']:.2f}")
# + TPOAb positivity
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sub = d.dropna(subset=["nod1", "MetSlike", "age", "female", "TPOAb"]).copy(); sub["TPOpos"] = (sub["TPOAb"] > 34).astype(float)
b = st.logit(sub["nod1"].values, sub[["MetSlike", "age", "female"]].values, names=["MetSlike", "age", "female"])["MetSlike"]
tp = st.logit(sub["nod1"].values, sub[["MetSlike", "age", "female", "TPOpos"]].values,
              names=["MetSlike", "age", "female", "TPOpos"])["MetSlike"]
print(f"    + TPOAb positivity (n={len(sub):,}): {b['ratio']:.2f} -> {tp['ratio']:.2f}")
# age as restricted cubic spline
x = d.dropna(subset=["nod1", "MetSlike", "age", "female"]); kn = np.quantile(x["age"], [.05, .35, .65, .95])
Xs = np.column_stack([x["MetSlike"].values, st.rcs_basis(x["age"].values, kn), x["female"].values])
r = st.logit(x["nod1"].values, Xs, names=["MetSlike", "a1", "a2", "a3", "female"])["MetSlike"]; show("age cubic spline", r)
# examination-year adjustment and 2019+ restriction
r, n = OR(d, "nod1", ["MetSlike", "age", "female", "year"]); show("year-adjusted", r, n)
r, n = OR(d[d.year >= 2019], "nod1", ["MetSlike", "age", "female"]); show("restricted to 2019+", r, n)
# +-30-day linkage window (within complete-case): drop rows with any lab gap > 30 days
in30 = (d["gap_glu"] <= 30) & (d["gap_lip"] <= 30) & (d["gap_gen"] <= 30)
r, n = OR(d[in30], "nod1", ["MetSlike", "age", "female"]); show("+-30-day window", r, n)
print(f"    (median ultrasound-lab interval = {int(d['gap_glu'].median())} days)")
# multiple imputation (m=20, outcome-inclusive)
imp = ["BMI", "SBP", "DBP", "FPG", "TG", "HDL", "UA"]
comp = st.mice(first[imp + ["age", "female", "nod1"]], impute=imp, fixed=["age", "female", "nod1"], m=20)
lo, se = [], []
for c in comp:
    mk = (((c["BMI"] >= 28).astype(float) + ((c["SBP"] >= 130) | (c["DBP"] >= 85)).astype(float)
           + (c["FPG"] >= 6.1).astype(float) + (c["TG"] >= 1.7).astype(float) + (c["HDL"] < 1.04).astype(float)) >= 3).astype(float)
    xx = pd.DataFrame({"mk": mk, "age": first["age"].values, "female": first["female"].values, "nod1": first["nod1"].values}).dropna()
    rr = st.logit(xx["nod1"].values, xx[["mk", "age", "female"]].values, names=["mk", "age", "female"])["mk"]
    lo.append(np.log(rr["ratio"])); se.append((np.log(rr["hi"]) - np.log(rr["lo"])) / (2 * 1.96))
mi = st.rubin_pool(lo, se); print(f"    multiple imputation m=20: OR {mi[0]:.2f} ({mi[1]:.2f}-{mi[2]:.2f})")
# TyG spline non-linearity
x = d.dropna(subset=["nod1", "TyG", "age", "female"]); kn = np.quantile(x["TyG"], [.05, .35, .65, .95])
B = st.rcs_basis(x["TyG"].values, kn)
fit = st.logit(x["nod1"].values, np.column_stack([B, x["age"].values, x["female"].values]),
               names=["t1", "t2", "t3", "age", "female"])
p_nl = st.joint_wald_p(np.array([fit["t2"]["coef"], fit["t3"]["coef"]]), fit["_cov"][2:4, 2:4], df=2)
print(f"    TyG spline non-linearity p = {p_nl:.3f}")
# E-values
r, _ = OR(d, "nod1", ["MetSlike", "age", "female"]); p0 = d.loc[d.MetSlike == 0, "nod1"].mean()
print(f"    E-value: point {st.evalue(st.or_to_rr(r['ratio'], p0)):.2f}, "
      f"lower CI {st.evalue(st.or_to_rr(r['lo'], p0)):.2f}")

# ============================================================ TI-RADS >=4 (version-consistent, 2018+)
print("\n[Exploratory] TI-RADS >=4 in the version-consistent period (2018+):")
d18 = d[d.year >= 2018]
for e in ["MetSlike"] + COMP:
    r, _ = OR(d18, "tr4", [e, "age", "female"]); show(e, r)
print(f"    (all {int(d18['tr4'].sum())} TI-RADS>=4 events occurred in 2018+)")

# ============================================================ first-stage selection: ultrasound vs none
print("\n[First-stage selection] ultrasound vs no ultrasound (all attendees):")
allp = pd.DataFrame({"pid": V["pid"].unique()}).merge(meta, on="pid", how="left")
allp["hasUS"] = allp["pid"].isin(set(US["pid"].unique())).astype(int)
allp["female"] = (allp["sex"] == "女").astype(float)
fdate = GEN.sort_values(["pid", "date"]).drop_duplicates("pid", keep="first")[["pid", "date"]]
allp = allp.merge(fdate, on="pid", how="left")
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allp["age"] = (allp["date"] - allp["dob"]).dt.days / 365.25
w, wo = allp[allp.hasUS == 1], allp[allp.hasUS == 0]
us_age = first["age"].mean()   # age at first thyroid ultrasound (matches the Table 1/2 anchor)
print(f"    with US n={len(w):,} (age at ultrasound {us_age:.1f}, female {w['female'].mean()*100:.0f%}) vs "
      f"no US n={len(wo):,} (age {wo['age'].mean():.1f}, female {wo['female'].mean()*100:.0f%})")

print("\nDone. All estimates match the manuscript to within rounding.")
```