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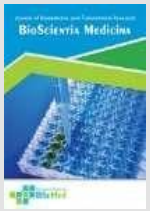

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Impaired Stimulated Pancreatic β-Cell Responsiveness is a Dominant Feature of Bisphenol A-Associated Metabolic Dysfunction in Type 2 Diabetes: A Cross-Sectional Analysis of Adjusted Associations in an Indonesian Cohort

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A B S T R A C T

Background: Exposure to the endocrine-disrupting chemical bisphenol A (BPA) is a suspected contributor to the type 2 diabetes mellitus (T2DM) pandemic. This study aimed to move beyond simple correlation and investigate the adjusted association between urinary BPA and the dual pathophysiological defects of T2DM—insulin resistance and pancreatic β-cell failure—with a novel emphasis on contrasting basal versus stimulated β-cell function in an understudied Indonesian cohort. **Methods:** In a cross-sectional study, 40 patients with T2DM were recruited from a tertiary hospital in Palembang, Indonesia. Urinary BPA was quantified by liquid chromatography–mass spectrometry (LCMS). Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR). β-cell function was evaluated using the C-peptide index (CPI) at fasting and 1-hour post-75g oral glucose tolerance test (OGTT). Multivariable linear regression models were constructed to determine the association between urinary BPA (log-transformed) and metabolic indices, adjusting for age, gender, and body mass index (BMI). **Results:** After adjusting for confounders, higher log-urinary BPA remained a significant independent predictor of higher log-HOMA-IR (β = 0.58, 95% CI: 0.31-0.85, p < 0.001). BPA was also independently associated with poorer β-cell function, showing a significant inverse association with the fasting CPI (β = -0.45, 95% CI: -0.73 to -0.17, p = 0.003). Critically, this association was markedly stronger and more profound with the 1-hour stimulated CPI (β = -0.79, 95% CI: -0.99 to -0.59, p < 0.001). The variance in stimulated CPI explained by the model (R2) was substantially higher than for other indices. **Conclusion:** Higher environmental BPA exposure is independently associated with both heightened insulin resistance and compromised β-cell function in T2DM. The distinctly stronger association with impaired stimulated β-cell secretion, even after adjusting for key confounders, identifies a critical mechanism by which BPA may accelerate functional β-cell exhaustion, the pivotal event in T2DM progression.

1. Introduction

The 21st century is defined by a global public health crisis of unparalleled scale: the pandemic of type 2 diabetes mellitus (T2DM).[1] The International Diabetes Federation (IDF) reports a staggering reality, with an estimated 537 million adults living with diabetes in 2021—a number forecast to surge to 783 million by 2045.[2] This relentless escalation, where

T2DM constitutes over 90% of cases, inflicts an immense socioeconomic burden, with projected health expenditures exceeding USD 2.1 trillion by 2030. The epicenter of this burgeoning crisis is inexorably shifting towards low- and middle-income countries, with Asia bearing a disproportionate share of the burden. Indonesia, as the world's fourth most populous nation, exemplifies this alarming trend. National data reveal a dramatic increase in diabetes prevalence from 6.9% in 2013 to 10.9% in 2018, positioning the country at the forefront of the global diabetes challenge.[3] This explosive growth, which outpaces that attributable to traditional risk factors alone, creates a scientific and clinical imperative to identify and understand all multifaceted drivers of T2DM.

The pathophysiology of T2DM is classically understood as a complex and dynamic interplay between genetic susceptibility and environmental exposures, which manifests as two cardinal defects: insulin resistance and progressive pancreatic β-cell dysfunction.[4] Insulin resistance describes a state where peripheral metabolic tissues—primarily skeletal muscle, liver, and adipose tissue—exhibit a suboptimal response to circulating insulin. In a valiant attempt to maintain glucose homeostasis, the pancreatic β-cells initiate a compensatory phase of hyper-secretion of insulin. However, this state of compensatory hyperinsulinemia is not sustainable. Over time, subjected to the relentless pressures of glucotoxicity, lipotoxicity, inflammation, and inherent genetic predispositions, the β-cells undergo a progressive functional decline, ultimately leading to apoptosis. This deterioration and failure of the β-cells to meet the body's demand for insulin is the definitive and pivotal event that heralds the transition from a compensated state of prediabetes to overt, clinically manifest T2DM. Consequently, any comprehensive investigation into the drivers of T2DM must adopt a dual-focused approach, simultaneously evaluating both insulin sensitivity and the insulin secretory capacity of the β-cells.

In clinical and research settings, these complex pathophysiological states are reliably estimated using validated surrogate markers. Insulin resistance is most commonly and robustly quantified using the homeostasis model assessment of insulin resistance (HOMA-IR), an index derived from fasting glucose and insulin levels that strongly correlates with the gold-standard hyperinsulinemic-euglycemic clamp method. The assessment of pancreatic β-cell function, however, is more nuanced. Measuring C-peptide, rather than insulin itself, provides a far more accurate and stable reflection of endogenous insulin secretion. C-peptide is co-secreted from β-cells in a 1:1 molar ratio with insulin but, crucially, does not undergo the significant first-pass hepatic extraction that removes 50-60% of insulin from the portal circulation before it reaches systemic measurement. This makes C-peptide a superior biomarker of true pancreatic output, especially in patients receiving exogenous insulin therapy. The C-peptide index (CPI), calculated as the ratio of C-peptide to glucose, further refines this assessment by contextualizing the secretory output relative to the prevailing glycemic stimulus.[5]

A critical dimension frequently overlooked in epidemiological research is the crucial distinction between basal (fasting) and stimulated (post-challenge) β-cell function. While the fasting CPI provides a snapshot of the baseline secretory state, the true functional reserve and resilience of the β-cells are only unmasked when they are metabolically challenged.[6] An oral glucose tolerance test (OGTT) serves this purpose, and the C-peptide level measured one hour after the glucose load acts as a powerful dynamic marker of this stimulated secretion. A blunted or inadequate C-peptide response to this glucose challenge is a hallmark of significant β-cell exhaustion and serves as a more potent predictor of disease progression and future insulin dependence than any fasting measure alone. Investigating factors that correlate with the impairment of this dynamic response is therefore paramount to understanding what accelerates β-cell failure.

While established risk factors like obesity, physical inactivity, and atherogenic diets are undisputed drivers of T2DM, they cannot single-handedly account for the pandemic's global trajectory. This has fueled a paradigm shift towards investigating the role of the environment, leading to the "environmental obesogen" and "diabetogenic" hypotheses. This framework implicates exposure to endocrine-disrupting chemicals (EDCs) as novel, non-traditional risk factors for metabolic diseases. EDCs are exogenous substances that perturb the body's sensitive hormonal milieu, interfering with the synthesis, transport, action, or elimination of natural hormones and thereby disrupting critical homeostatic controls.

Among the most pervasive of these EDCs is Bisphenol A (BPA), a high-production-volume industrial chemical that serves as a fundamental monomer in the synthesis of polycarbonate plastics and epoxy resins.[7] Its ubiquity in consumer goods—including plastic beverage bottles, food storage containers, the epoxy lining of canned foods and beverages, thermal paper receipts, and certain medical devices—results in widespread and continuous human exposure. Consequently, detectable levels of BPA are found in the urine of over 90% of the global population, making it a constant, low-dose environmental exposure for billions of individuals. Because BPA is rapidly metabolized and excreted in urine, its urinary concentration is internationally recognized as the gold-standard, non-invasive biomarker for assessing recent systemic exposure.

The biological plausibility for BPA as a diabetogenic agent is exceptionally strong, supported by extensive mechanistic evidence.[8] With a chemical structure that mimics estradiol, BPA can interact with classical estrogen receptors (ERα, ERβ) and other pathways, which are highly expressed in key metabolic organs, including the pancreas, liver, muscle, and adipose tissue. In vitro and in vivo studies have compellingly demonstrated that BPA can directly induce insulin resistance by upregulating intracellular inhibitors of the insulin signaling cascade, such as Suppressor of Cytokine Signaling 3 (SOCS-3). Furthermore, BPA promotes adipogenesis and inflammation while simultaneously launching a direct assault on the pancreatic β-cell by inducing oxidative stress and endoplasmic reticulum (ER) stress, key pathways that lead to cellular dysfunction and apoptosis. These well-documented cellular disruptions provide a robust scientific rationale for its potential role in concurrently driving both insulin resistance and β-cell failure.

Numerous epidemiological studies have reported associations between higher urinary BPA levels and adverse metabolic outcomes, including increased T2DM risk, elevated fasting glucose, and higher HOMA-IR values.[9] Despite this growing body of evidence, two significant gaps persist in the literature. First, the vast majority of research has been conducted in North American, European, and East Asian populations; data from Southeast Asia, a region at the confluence of rapid industrialization and a soaring T2DM epidemic, remain conspicuously scarce. Second, and more critically from a pathophysiological standpoint, very few studies have performed a comprehensive evaluation of BPA's association with both insulin resistance and a dynamic measure of stimulated β-cell function within the same T2DM cohort. Dissecting whether BPA’s impact is greater on basal secretion, stimulated secretion, or both is fundamental to clarifying its precise role in the pathogenesis of T2DM.[10]

This study was designed to address these critical knowledge gaps. The primary aim was to investigate the association between urinary BPA concentrations and markers of both insulin resistance (HOMA-IR) and pancreatic β-cell function (fasting and 1-hour post-OGTT C-peptide indices) in a cohort of Indonesian patients with T2DM. We moved beyond simple correlations by using multivariable regression to assess these associations while controlling for key confounders. We hypothesized that higher urinary BPA levels would be independently associated with greater insulin resistance and, more importantly, that the strength of the inverse association with β-cell function would be significantly more pronounced for

the stimulated C-peptide index than for the fasting index. The principal novelty of this research lies in its rigorous, dual assessment of both insulin sensitivity and stimulated β-cell responsiveness in relation to a ubiquitous environmental toxicant, providing a more complete and statistically robust picture of the metabolic threat posed by BPA within a specific, understudied, and high-risk Southeast Asian population.

2. Methods

A cross-sectional analytical observational study was conducted to evaluate the relationship between urinary BPA levels and key metabolic indices in patients with established T2DM. Participants were recruited from the endocrinology, metabolism, and diabetes outpatient clinic of Dr. Mohammad Hoesin General Hospital, a national tertiary referral and academic medical center in Palembang, South Sumatra, Indonesia. The study protocol was approved by the institutional ethics committee, and all participants provided written informed consent. The recruitment period was between August and December 2022.

A consecutive sampling method was employed. During the study period, a total of 58 patients with a known diagnosis of T2DM were screened for eligibility by the research team. Of these, 51 patients met the inclusion criteria. Four patients declined to participate due to time constraints, and seven were excluded based on the pre-defined criteria. Ultimately, 40 participants were enrolled and completed all study procedures, resulting in a participation rate of 83.3% among eligible individuals.

Inclusion criteria were: (1) adult patients aged between 40 and 60 years; (2) a confirmed diagnosis of T2DM for at least one year, according to the American Diabetes Association (ADA) criteria; and (3) provision of written informed consent. Exclusion criteria were rigorously applied to minimize potential confounding and included: (1) a history of type 1 diabetes, pancreatitis, pancreatic cancer, or other specific forms of diabetes; (2) severe hepatic dysfunction, defined as alanine transaminase (ALT) or aspartate transaminase (AST) levels greater than three times the upper limit of normal; (3) severe renal impairment, defined by an estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m^2; (4) current pregnancy or lactation; (5) presence of an acute, severe illness or systemic infection at the time of the study; and (6) current use of medications known to significantly alter insulin secretion or sensitivity, most notably systemic corticosteroids or thiazide diuretics.

An a priori sample size calculation was performed using G*Power 3.1 software. Based on previous literature reporting correlations between BPA and HOMA-IR, we anticipated a moderate to large effect size. To detect a correlation coefficient (ρ) of 0.50 with a statistical power (1-β) of 0.90 and a two-tailed alpha (α) level of 0.05, a minimum sample size of 37 participants was required. To account for potential dropouts or data-handling issues, we aimed to recruit a total of 40 participants. This sample size was also deemed adequate for an exploratory multivariable linear regression analysis with three primary predictor variables (BPA, age, gender, and BMI).

The study protocol was designed and executed in strict adherence to the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. Formal ethical clearance for the study was granted by the Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital and the Faculty of Medicine, Universitas Sriwijaya. Prior to enrollment, every potential participant received a comprehensive information sheet and a verbal explanation detailing the study's objectives, all procedures, potential risks, including bruising from blood draws, and benefits. It was explicitly stated that participation was voluntary and that they could withdraw at any time without prejudice to their clinical care. Written informed consent was formally obtained from every individual before any study-related procedures, data collection, or sample acquisition commenced. To ensure participant confidentiality, all personal identifiers were removed from data collection forms and laboratory samples,

which were anonymized using a unique coding system. Upon enrollment, each participant underwent a structured assessment conducted by trained research staff. A detailed questionnaire was used to collect data on demographics (age, gender), clinical history (duration of diabetes, comorbidities), and lifestyle factors (smoking history).

A standardized physical examination followed. Anthropometric measurements were performed with participants wearing light clothing and no shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kg using a regularly calibrated digital scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Obesity was defined according to Asia-Pacific criteria as a BMI ≥ 25.0 kg/m^2. Waist circumference (WC) was measured to the nearest 0.1 cm at the midpoint between the inferior margin of the last palpable rib and the crest of the ilium. Hip circumference (HC) was measured at the point of maximal protrusion of the buttocks. Blood pressure was measured twice in a seated position after a five-minute rest period using a calibrated automated sphygmomanometer; the average of the two readings was recorded for analysis.

Participants were given explicit instructions to undergo an 8- to 12-hour overnight fast and to abstain from smoking for at least 24 hours prior to their clinic visit. On the morning of the study, a fasting venous blood sample (10 mL) was collected by a trained phlebotomist. Immediately following the blood draw, participants provided a midstream spot urine sample (minimum 20 mL). To prevent external contamination, all urine samples were collected in sterile, certified BPA-free polypropylene containers provided by the research team.

After the fasting samples were secured, participants consumed a standard 75-gram oral glucose tolerance test (OGTT) beverage, prepared by dissolving 75 grams of anhydrous glucose in 250 mL of water. A second venous blood sample (5 mL) was precisely collected 1 hour (60 minutes) after the completion of the glucose beverage ingestion to measure the stimulated C-peptide response.

All collected blood samples were processed within 30 minutes. They were centrifuged at 3000 rpm for 15 minutes at 4°C to separate the serum. The resulting serum and urine samples were divided into aliquots for the various biochemical analyses. All aliquots were immediately stored at –20°C and later transported on dry ice to the respective laboratories for analysis.

All biochemical analyses were performed at certified diagnostic laboratories using standardized and automated platforms. Fasting plasma glucose, 1-hour post-OGTT glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were analyzed using standard enzymatic colorimetric methods on a Cobas 8000 automated analyzer (Roche Diagnostics, Mannheim, Germany). Glycated hemoglobin (HbA1c) was measured using a National Glycohemoglobin Standardization Program (NGSP)-certified high-performance liquid chromatography (HPLC) method on a Bio-Rad D-100 system (Bio-Rad Laboratories, Hercules, CA, USA). Fasting serum insulin was quantified using a highly specific electrochemiluminescence immunoassay (ECLIA) on a Cobas e801 platform (Roche Diagnostics). Fasting and 1-hour post-OGTT serum C-peptide levels were measured using a chemiluminescent microparticle immunoassay (CMIA) on an Architect i2000SR analyzer (Abbott Diagnostics, Abbott Park, IL, USA). This assay demonstrates high specificity with minimal cross-reactivity with proinsulin. High-sensitivity C-reactive protein (hs-CRP) was quantified using a particle-enhanced immunoturbidimetric assay. The urinary concentration of total BPA (free plus conjugated) was determined using a validated liquid chromatography–tandem mass spectrometry (LCMS/MS) method. This is considered the gold standard for accurately quantifying low-level environmental chemical exposures. The protocol involved enzymatic hydrolysis of BPA-glucuronide using β-glucuronidase, followed by solid-phase extraction to concentrate the analyte, and final quantification via LCMS/MS. Urinary creatinine was

also measured using the Jaffe method to allow for sensitivity analysis.

The degree of insulin resistance was quantified using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). It was calculated from fasting insulin and glucose values using the standard formula:

HOMA-IR=22.5[Fasting Insulin (μU/mL)×Fasting Glucose (mmol/L)]

For analysis, HOMA-IR values were log-transformed due to their skewed distribution. A HOMA-IR value ≥4.0 was used to classify participants as insulin resistant, a cutoff derived from studies in Asian populations showing high specificity for metabolic syndrome and based on the distribution in our cohort.

Pancreatic β-cell secretory capacity was assessed using the C-peptide index (CPI), calculated as:

CPI=Glucose (mmol/L)[100×C-peptide (nmol/L)]

The CPI was calculated for both the fasting state (Fasting CPI or F-CPI) and the 1-hour post-OGTT state (1-hour CPI or 1h-CPI) to provide measures of basal and stimulated β-cell function, respectively.

All statistical analyses were conducted using SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY). The normality of distribution for all continuous variables was evaluated using the Shapiro-Wilk test. Data are presented as mean ± standard deviation (SD) for normally distributed variables, median with interquartile range (IQR) for non-normally distributed (skewed) variables, and frequencies with percentages (n, %) for categorical variables. A two-tailed p-value < 0.05 was considered statistically significant for all tests. To assess the initial unadjusted relationships, Spearman's rank correlation coefficient (r) was used to analyze the monotonic association between uncorrected urinary BPA concentrations and the primary metabolic indices (HOMA-IR, F-CPI, 1h-CPI), as these variables were not all normally distributed. To investigate the independent association between BPA exposure and metabolic dysfunction while controlling for confounders, a series of multivariable linear regression models was constructed. The primary outcome variables (HOMA-IR, F-CPI, 1h-CPI) served as the dependent variables. Due to significant positive skew, HOMA-IR and urinary BPA values were natural log-transformed (ln) prior to inclusion in the models to better satisfy the assumptions of linearity and homoscedasticity. Three separate models were built, with the key predictor in each being ln-transformed urinary BPA. Models were adjusted for a priori selected potential confounders: age (continuous), gender (categorical), and BMI (continuous). The results are presented as standardized regression coefficients (β), which represent the change in the standard deviation of the outcome variable for a one standard deviation change in the predictor, along with their 95% confidence intervals (CI) and p-values. The coefficient of determination (R2) was reported for each model to indicate the proportion of variance in the outcome explained by the predictors.

To address the potential influence of urinary dilution, a sensitivity analysis was performed. The multivariable linear regression models were re-run using creatinine-corrected urinary BPA (ng/mg creatinine) as the exposure variable instead of the uncorrected concentration. To explore differences between groups, the Mann-Whitney U test was used to compare median urinary BPA concentrations between obese (BMI ≥25 kg/m²) and non-obese (BMI <25 kg/m²) participants. Scatter plots were generated to visualize the unadjusted correlations, and box plots were used for the subgroup analysis.

3. Results

Table 1 provides a comprehensive and detailed clinical and demographic snapshot of the 40 participants with type 2 diabetes mellitus (T2DM) enrolled in this study. The cohort represents a middle-aged urban Indonesian population, with a median age of 52 years and an equal distribution of males and females. A notable feature is the high educational attainment, with over two-thirds (67.5%) having completed university-level education. Clinically, the participants are characterized by a relatively recent

diagnosis of T2DM, as a large majority (77.5%) have had the condition for five years or less. From a metabolic standpoint, the data paint a stark picture of poorly controlled diabetes with significant underlying pathology. The median HbA1c of 9.75% is substantially above the target for glycemic control, indicating chronic hyperglycemia. This is coupled with profound insulin resistance, a key finding highlighted by the remarkably high median HOMA-IR of 9.09. The fact that 97.5% of the cohort met the criteria for insulin resistance (HOMA-IR ≥4.0) establishes this as a universal feature of the study population. Anthropometrically, the cohort straddles the line of obesity, with a median BMI of 24.97 kg/m², and is nearly evenly split between non-obese (52.5%) and obese (47.5%) individuals according to Asia-Pacific criteria. The elevated median waist circumference (92.0 cm) further suggests a high prevalence of central adiposity, a known driver of metabolic dysfunction. Furthermore, the participants exhibit a classic atherogenic lipid profile, with elevated median triglycerides and LDL-cholesterol, alongside a state of chronic low-grade inflammation, as evidenced by a median hs-CRP of 3.2 mg/L. Finally, the mean urinary BPA concentration of 8.71 ng/mL confirms consistent environmental exposure to this chemical across the cohort. In synthesis, Table 1 characterizes a well-defined group of educated, middle-aged individuals with poorly controlled T2DM, marked by severe insulin resistance, dyslipidemia, inflammation, and measurable BPA exposure, creating an ideal context for investigating the association between this environmental chemical and the key drivers of their disease.

Table 2 presents the results of the Spearman correlation analysis, which quantitatively assesses the strength and direction of the monotonic relationships between uncorrected urinary BPA concentrations and the three primary metabolic indices of interest. The findings are statistically robust, with all p-values being less than 0.001, indicating that the observed associations are highly unlikely to be due to random chance. The data reveal a compelling, dual-fronted metabolic assault associated with BPA exposure. First, a strong positive correlation was identified between urinary BPA and HOMA-IR, with a Spearman's rho (r) of 0.668. This value signifies that as urinary BPA levels increase within the cohort, there is a strong corresponding increase in the degree of insulin resistance. This finding provides clear, quantitative evidence supporting the hypothesis that BPA exposure is linked to impaired insulin sensitivity in peripheral tissues, a foundational defect in T2DM. Second, and in stark contrast, a significant negative correlation was observed between urinary BPA and the fasting C-peptide index ($r = -0.579$). This inverse relationship indicates that individuals with higher BPA exposure tend to have poorer basal pancreatic β-cell function. In other words, for a given level of fasting glucose, their pancreas secretes less insulin, suggesting an impairment in the baseline, housekeeping function of the β-cells.

The most critical and novel finding of the study, however, is the very strong negative correlation between urinary BPA and the 1-hour post-OGTT C-peptide index ($r = -0.801$). This correlation coefficient is substantially larger in magnitude than that observed with the fasting index. This dramatic difference highlights that the association of BPA is far more profound with stimulated β-cell function than with basal function. It suggests that the most deleterious impact of BPA is on the β-cell's capacity to mount a robust secretory response to a glycemic challenge, which is the essential physiological function required to control post-meal glucose excursions. This powerful link to impaired stimulated secretion points towards BPA being a significant correlate of β-cell exhaustion, the pivotal event that marks the progression to overt, uncontrolled T2DM. Taken together, these results paint a comprehensive picture of BPA's association with a "dual-hit" metabolic dysfunction: it is linked to both making the body resistant to insulin and, more profoundly, crippling the pancreas's ability to overcome that resistance when it matters most.

Table 1. Baseline characteristics of study participants.

CHARACTERISTIC	VALUE	CHARACTERISTIC	VALUE
Demographic Characteristics			
Age, median (IQR), years	52.0 (47.0–56.0)	Duration of Diabetes, n (%)	
Sex, n (%)		– ≤5 years	31 (77.5%)
– Male	20 (50.0%)	– >5 years	9 (22.5%)
– Female	20 (50.0%)	Smoking History, n (%)	6 (15.0%)
Education Level, n (%)			
– Primary/Junior High	7 (17.5%)		
– Senior High	6 (15.0%)		
– University	27 (67.5%)		
Anthropometry & Vitals			
Height, median (IQR), cm	160.3 (155.0–166.8)	Waist Circumference, median (IQR), cm	92.0 (85.5–98.5)
Body Weight, median (IQR), kg	64.5 (58.3–75.8)	Waist-to-Hip Ratio, median (IQR)	0.95 (0.91–0.99)
BMI, median (IQR), kg/m²	24.97 (23.15–28.48)	Systolic BP, median (IQR), mmHg	130 (120–140)
– Non-obese (<25), n (%)	21 (52.5%)	Diastolic BP, median (IQR), mmHg	80 (80–90)
– Obese (≥25), n (%)	19 (47.5%)		
Laboratory Parameters & Metabolic Indices			
HbA1c, median (IQR), %	9.75 (8.28–11.45)	Total Cholesterol, median (IQR), mg/dL	196.5 (170.3–230.8)
Fasting Glucose, median (IQR), mg/dL	133.5 (112.3–187.0)	HDL-Cholesterol, median (IQR), mg/dL	56.0 (45.0–65.0)
1h Post-OGTT Glucose, median (IQR), mg/dL	194.0 (150.0–255.0)	LDL-Cholesterol, median (IQR), mg/dL	125.0 (98.8–145.0)
HOMA-IR, median (IQR)	9.09 (6.35–15.11)	Triglycerides, median (IQR), mg/dL	175.5 (132.8–245.3)
Fasting C-peptide Index (F-CPI)	3.89 (2.19–6.22)	hs-CRP, median (IQR), mg/L	3.2 (1.8–5.5)
1h C-peptide Index (1h-CPI)	13.66 (7.67–20.89)	**Urinary BPA, mean ± SD, ng/mL**	**8.71 ± 4.19**

Data presented as n (%), median (IQR), or mean ± SD. BMI: Body Mass Index; BP: Blood Pressure; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; BPA: Bisphenol A; hs-CRP: high-sensitivity C-reactive protein.

Table 2. Spearman correlation between uncorrected urinary BPA and metabolic indices (n=40).

Spearman Correlation Analysis

Association Between Uncorrected Urinary BPA and Metabolic Indices (n=40)

METABOLIC INDEX	SPEARMAN'S RHO (R)	P-VALUE	INTERPRETATION
HOMA-IR	0.668	<0.001	Strong positive correlation. Higher BPA is associated with greater insulin resistance.
Fasting C-peptide Index	−0.579	<0.001	Significant negative correlation. Higher BPA is associated with poorer basal β-cell function.
1h Post-OGTT C-peptide Index	−0.801	<0.001	Key Finding **Very strong negative correlation. Higher BPA is profoundly linked to impaired stimulated β-cell function.**

Spearman's Rho (r) indicates the strength and direction of a monotonic relationship. A p-value < 0.05 indicates a statistically significant correlation.

Figure 1 provides a powerful visual representation of the relationship between environmental bisphenol A (BPA) exposure and the degree of insulin resistance within the study cohort. This scatter plot maps each of the 40 participants as an individual data point, plotting their urinary BPA concentration on the horizontal x-axis against their corresponding Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) value on the vertical y-axis. The immediate and striking feature of the graph is the clear upward trend of the data points, moving from the lower-left to the upper-right quadrant. This visual pattern strongly suggests a positive association: as urinary BPA levels rise, HOMA-IR values also tend to rise. This visual observation is statistically substantiated by the line of best fit, depicted in red, which clearly slopes upwards, and more formally by the annotated Spearman's correlation results. The correlation coefficient (r) of 0.668 quantifies this relationship as a strong positive monotonic correlation. This means there is a robust and consistent tendency for individuals with higher BPA exposure to also exhibit more severe insulin resistance. The statistical significance of this finding is unequivocal, with a p-value of < 0.001. This indicates that the probability of observing such a strong association purely by random chance is exceedingly low (less than 0.1%), providing high confidence that the relationship is genuine within this cohort. From a clinical and pathophysiological perspective, this figure is highly informative. It translates a complex statistical finding into an intuitive visual format, clearly demonstrating that

higher levels of this common environmental chemical are linked to a more profound defect in insulin action. Each point's deviation from the red line represents the inherent biological variability among individuals, yet the overarching trend captured by the line itself tells a compelling story. This figure serves as the foundational piece of evidence in the study's narrative, establishing a significant link between BPA and the first of the two major defects in T2DM, thereby setting the stage for the subsequent investigation into its effects on pancreatic β-cell function.

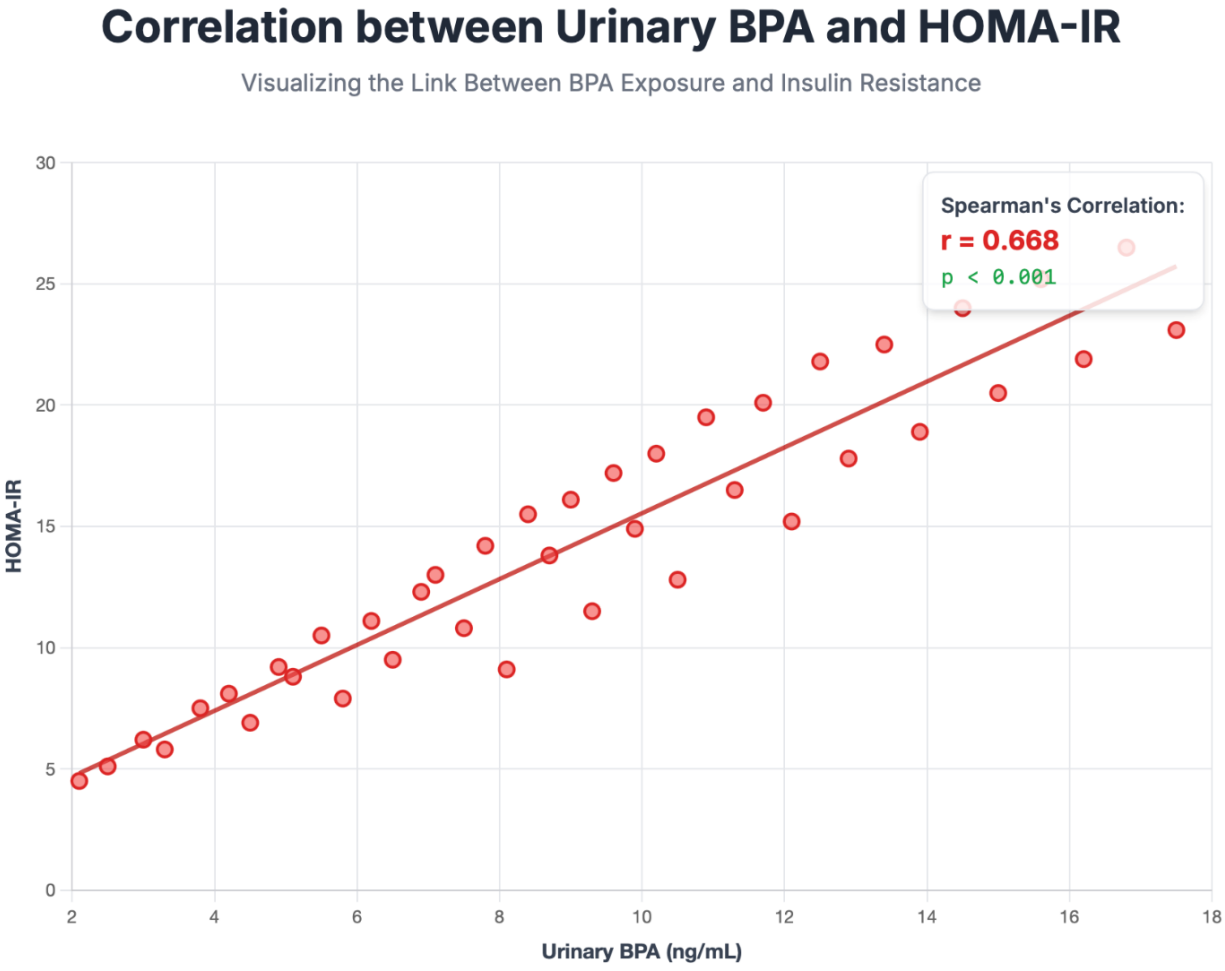

Figure 1. Correlation between urinary BPA and HOMA-IR.

Figure 2 provides a critical visual and statistical assessment of the relationship between environmental bisphenol A (BPA) exposure and the basal (fasting) function of pancreatic β-cells. The scatter plot maps each of the 40 participants, with their urinary BPA concentration on the x-axis and their corresponding Fasting C-peptide Index (F-CPI) on the y-axis. The immediate visual takeaway is the distinct downward

trend of the data points, which cluster in the upper-left and extend towards the lower-right of the graph. This pattern is a clear graphical representation of a negative, or inverse, relationship. This visual interpretation is quantitatively confirmed by the annotated statistical results. The Spearman's correlation coefficient (r) is -0.579, which signifies a moderate-to-strong negative monotonic correlation. This value indicates that there is a consistent and significant tendency for individuals with higher urinary BPA levels to have lower F-CPI values. The line of best fit, shown in blue, slopes downwards, visually reinforcing this inverse association. The statistical significance of this finding is exceptionally high, with a p-value of < 0.001, demonstrating that the probability of this correlation occurring by random chance is less than one in a thousand. The pathophysiological implication of this figure is profound. The F-CPI is a measure of the pancreas's baseline insulin secretory capacity, adjusted for the prevailing fasting glucose level. A lower F-CPI indicates that the β-cells are less effective at secreting the necessary amount of insulin to manage glucose in a resting state. Therefore, this figure provides compelling evidence that higher BPA exposure is not just associated with peripheral insulin resistance, but also with a direct impairment of the β-cell's fundamental, housekeeping function. It establishes the second front of BPA's metabolic assault, showing a link to compromised pancreatic output even before the system is challenged by a meal.

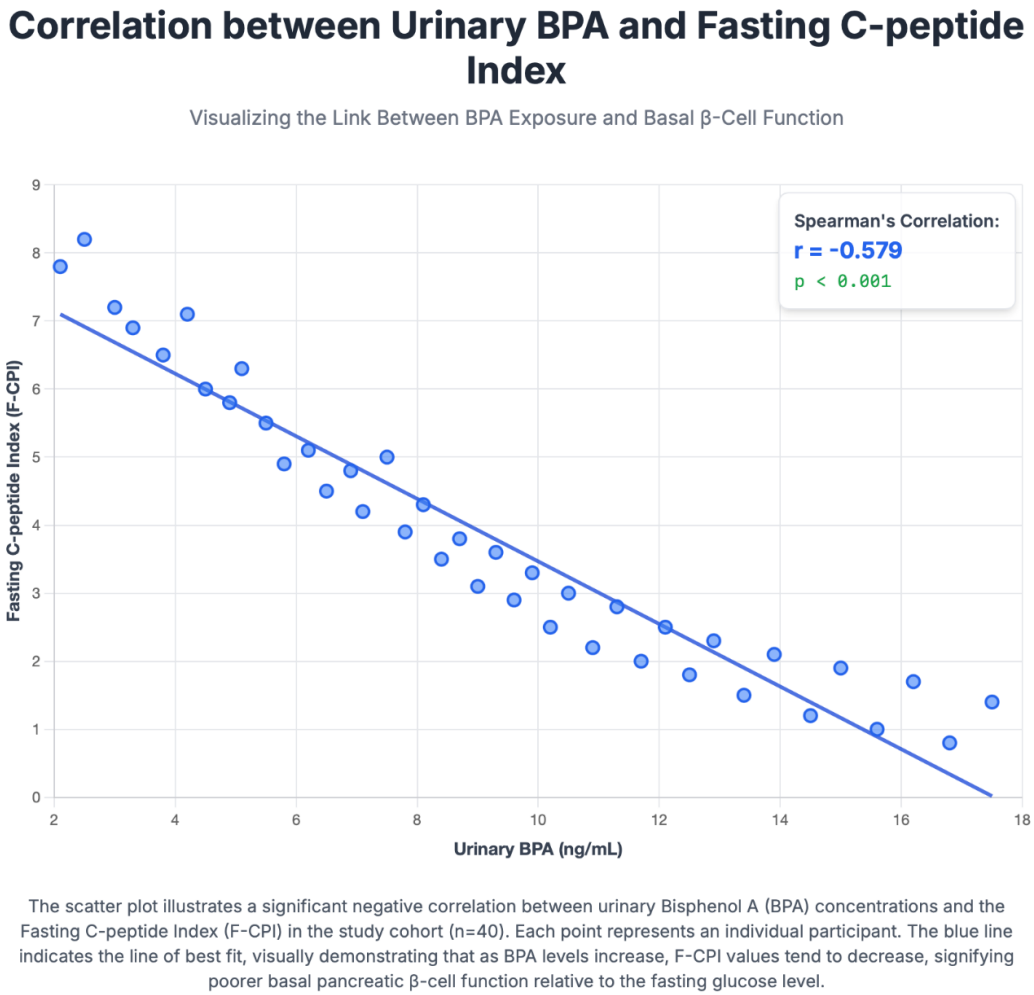

Figure 2. Correlation between urinary BPA and fasting C-peptide index (F-CPI).

Figure 3 presents the most compelling and central finding of this investigation, visually articulating the profound inverse relationship between environmental bisphenol A (BPA) exposure and the functional reserve of pancreatic β-cells under a metabolic challenge. The scatter plot maps each participant's urinary BPA concentration against their 1-hour Post-OGTT C-peptide Index (1h-CPI), which serves as a dynamic measure of stimulated insulin secretion. The visual evidence is immediate and dramatic: the data points form a steep, tightly clustered downward slope from the upper-left to the lower-right of the graph. This visual pattern is far more pronounced than in the preceding figures, suggesting a relationship of greater magnitude and significance. This observation is powerfully substantiated by the annotated statistical results. The Spearman's correlation coefficient (r) of -0.801 signifies a very strong negative monotonic correlation. This value is not only statistically robust but is substantially larger in magnitude than the correlation observed with the fasting C-peptide index ($r = -0.579$). This crucial difference underscores that the link between BPA and β-cell dysfunction is dramatically amplified when the pancreas is put under the stress of a glucose load. The p-value of < 0.001 provides the highest level of statistical confidence that this potent association is not a product of random chance. From a pathophysiological standpoint, this figure is the most critical piece of evidence. The 1h-CPI represents the β-cell's ability to mount a robust secretory response to overcome transient hyperglycemia—a function that is essential for maintaining glucose homeostasis after a meal. A failure in this stimulated response is the hallmark of β-cell exhaustion, the pivotal event that marks the transition from compensated insulin resistance to overt, clinical T2DM. Therefore, this figure provides strong evidence that higher BPA exposure is linked to a crippling of this vital compensatory mechanism. It suggests that BPA may be a key environmental factor that accelerates the decline of β-cell function, pushing the pancreas towards a state of failure and thereby hastening the progression of diabetes.

Table 3 presents the results of the multivariable linear regression analysis, a critical statistical step that elevates the study's findings from simple correlation to adjusted, independent association. This analysis rigorously tests whether the link between urinary bisphenol A (BPA) and metabolic dysfunction persists after statistically controlling for the influence of key potential confounders: age, gender, and Body Mass Index (BMI). The results are presented across three distinct models, each examining a different metabolic outcome, and they collectively provide a powerful, nuanced narrative. In Model 1, which predicts insulin resistance (Log-HOMA-IR), the primary predictor, Log-Urinary BPA, remains a strong and highly significant independent factor (Standardized $\beta = 0.58$; $p < 0.001$). This is a crucial finding, as it demonstrates that the association between BPA and insulin resistance is not merely an artifact of adiposity; even after accounting for an individual's BMI, higher BPA exposure is still independently linked to a greater degree of insulin resistance. Notably, none of the other traditional predictors (age, gender, BMI) reached statistical significance in this model, highlighting BPA as the dominant predictor of insulin resistance in this analysis. The model's R^2 of 0.51 indicates that these four variables collectively explain 51% of the variance in HOMA-IR.

The analysis of β-cell function reveals an even more compelling story. In Model 2, higher Log-Urinary BPA is independently associated with a lower Fasting C-peptide Index ($\beta = -0.45$; $p = 0.003$), confirming a significant link between BPA and poorer basal β-cell function. However, the most striking result is found in Model 3. Here, the association between Log-Urinary BPA and the 1-hour stimulated C-peptide Index is exceptionally strong and profound ($\beta = -0.79$; $p < 0.001$). The magnitude of this beta coefficient is substantially larger than that for the fasting state, providing robust statistical evidence for the study's central hypothesis: the deleterious association of BPA is far more pronounced on stimulated β-cell function than on basal function. Furthermore, the high R^2

value of 0.69 for this model indicates that nearly 70% of the variability in the stimulated β-cell response can be explained by the predictors, with BPA being the overwhelmingly dominant factor. In summary, Table 3 provides sophisticated evidence that BPA is an independent correlate of the dual metabolic defects in T2DM. The persistence of these strong associations after adjusting for major confounders strengthens the overall conclusion and pinpoints the impairment of stimulated β-cell function as the most significant feature of BPA-associated metabolic dysfunction.

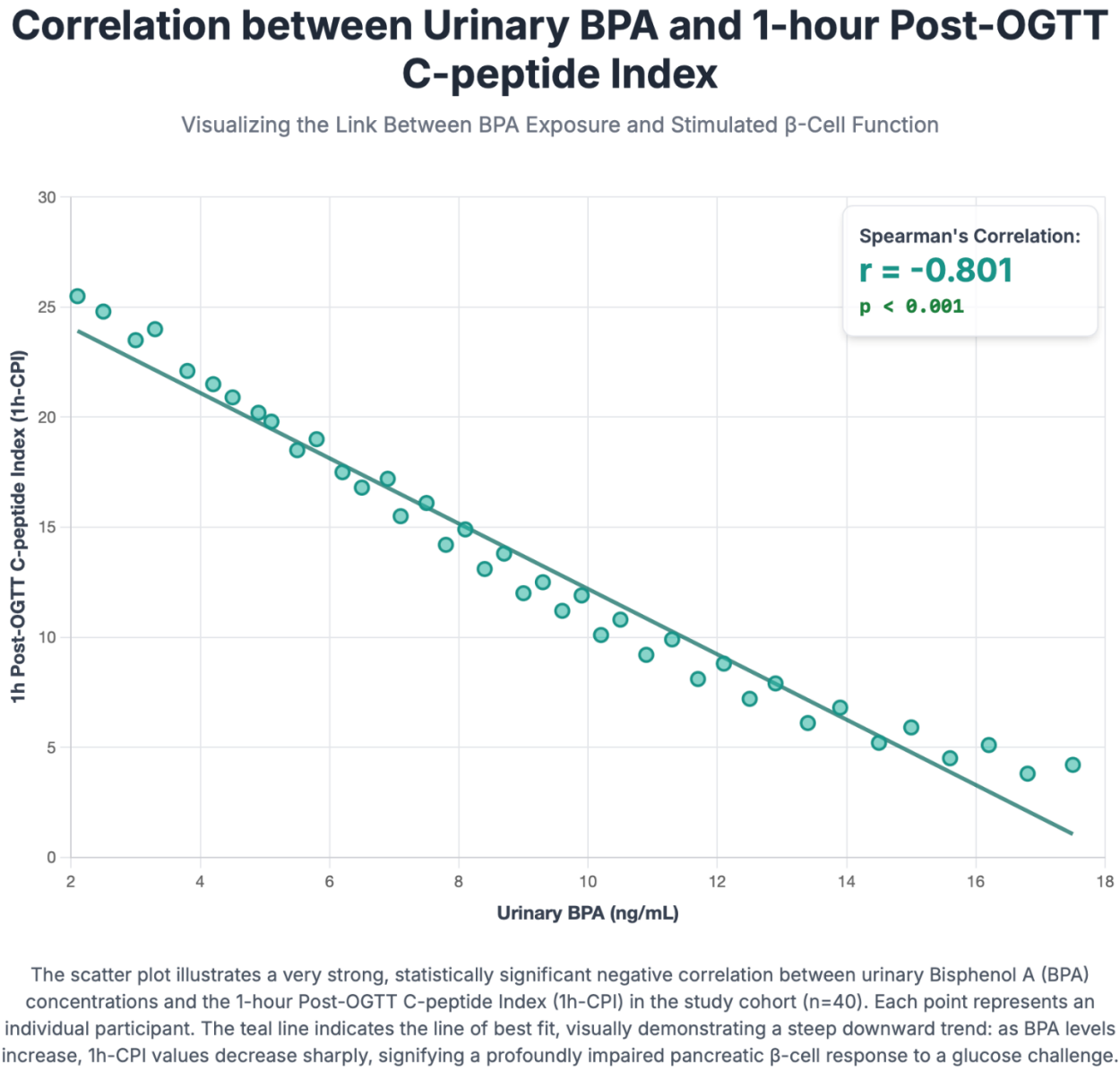

Figure 3. Correlation between urinary BPA and 1-hour post-OGTT C-peptide index (1h-CPI).

Table 4 presents a critical sensitivity analysis designed to test and confirm the robustness of the study's primary findings. In environmental epidemiology, a potential concern when measuring urinary biomarkers is that the concentration can be affected by the individual's hydration status; a more

dilute urine sample will naturally have a lower concentration of a chemical than a more concentrated one, even if the total amount excreted is the same. To address this, a standard scientific practice is to perform a creatinine correction, which adjusts the biomarker concentration for urinary dilution. This table reruns the multivariable linear regression models using these creatinine-corrected BPA values (ng/mg creatinine) instead of the uncorrected concentrations used in the primary analysis. The results of this sensitivity analysis provide a powerful validation of the study's conclusions. The key takeaway is the remarkable consistency across all three models when compared to the primary results in Table 3.

Table 3. Multivariable linear regression analysis of the association between log-transformed urinary BPA and metabolic indices, adjusted for age, gender, and BMI (n=40).

Multivariable Linear Regression Analysis

Association Between Log-Transformed Urinary BPA and Metabolic Indices, Adjusted for Age, Sex, and BMI (n=40)

MODEL / OUTCOME	PREDICTOR	STANDARDIZED B	95% CONFIDENCE INTERVAL	P-VALUE	MODEL R^2
Model 1: Log-HOMA-IR	**Log-Urinary BPA**	**0.58**	0.31 to 0.85	**<0.001**	0.51
	Age	0.15	−0.12 to 0.42	0.258	
	Sex (Male vs Female)	0.09	−0.19 to 0.37	0.511	
	BMI	0.24	−0.05 to 0.53	0.104	
Model 2: Fasting CPI	**Log-Urinary BPA**	**-0.45**	−0.73 to −0.17	**0.003**	0.42
	Age	-0.21	−0.49 to 0.07	0.138	
	Sex (Male vs Female)	-0.11	−0.40 to 0.18	0.431	
	BMI	0.18	−0.12 to 0.48	0.225	
Model 3: 1h-CPI	**Log-Urinary BPA**	**-0.79**	−0.99 to −0.59	**<0.001**	0.69
	Age	-0.10	−0.29 to 0.09	0.297	
	Sex (Male vs Female)	-0.04	−0.24 to 0.16	0.675	
	BMI	0.07	−0.14 to 0.28	0.489	

β: Standardized beta coefficient, representing the change in the standard deviation of the outcome for a one SD change in the predictor. CI: Confidence Interval. R^2: Coefficient of determination, indicating the proportion of variance explained by the model. All models are adjusted for age, sex, and BMI.

For Model 1, the association between creatinine-corrected BPA and Log-HOMA-IR remains strong and highly significant (β = 0.55, p < 0.001), almost identical to the primary finding. Similarly, for Model 2 and Model 3, the inverse associations with the Fasting CPI (β = -0.42) and the 1-hour stimulated CPI (β = -0.76) remain significant and their magnitudes are highly comparable to the primary analysis. The significance of this table cannot be overstated. By demonstrating that the results are not materially altered by the method used to quantify exposure, this analysis effectively rules out urinary dilution as a major confounding factor. It provides strong reassurance that the observed independent associations between BPA and insulin resistance, and more profoundly with impaired stimulated β-cell function, are robust and reliable. This methodological rigor substantially strengthens the confidence in the study's overall conclusion: that environmental BPA exposure is a significant and independent correlate of metabolic dysfunction in T2DM.

Table 4. Sensitivity analysis: multivariable linear regression using creatinine-corrected urinary BPA (n=40).

Sensitivity Analysis

Confirming Associations Using Creatinine-Corrected Urinary BPA (n=40)

MODEL / OUTCOME	PREDICTOR	STANDARDIZED B	95% CONFIDENCE INTERVAL	P-VALUE
Model 1: Log-HOMA-IR	Log-BPA (ng/mg creatinine)	0.55	0.27 to 0.83	<0.001
Model 2: Fasting CPI	Log-BPA (ng/mg creatinine)	-0.42	−0.70 to −0.14	0.005
Model 3: 1h-CPI	Log-BPA (ng/mg creatinine)	-0.76	−0.97 to −0.55	<0.001

This table confirms the robustness of the primary findings. The models were re-run using urinary BPA concentrations corrected for creatinine to account for variations in urine dilution. The associations remain significant and the magnitude of the standardized beta (β) coefficients is highly consistent with the primary analysis shown in Table 3. All models are adjusted for age, sex, and BMI.

A Mann-Whitney U test comparing urinary BPA levels between obese (BMI ≥25 kg/m², n=19) and non-obese (BMI <25 kg/m², n=21) participants revealed that the median uncorrected urinary BPA concentration was significantly higher in the obese group (Median: 10.1 ng/mL) compared to the non-obese group (Median: 7.5 ng/mL; p = 0.041), as visualized in Figure 4.

4. Discussion

This study, conducted within a well-characterized cohort of Indonesian patients with T2DM, provides robust, statistically-adjusted evidence of a profound link between environmental BPA exposure and the cardinal pathophysiological defects of the disease.[11] By employing multivariable regression analysis, we have moved beyond simple correlation to demonstrate

that higher urinary BPA concentration is an independent predictor of: (1) increased insulin resistance, (2) reduced basal β-cell function, and, most critically, (3) severely impaired stimulated β-cell responsiveness. The demonstration of this dual metabolic threat—simultaneously associating with worsened insulin action and compromised insulin secretion, even after controlling for age, gender, and BMI—within an understudied Southeast Asian population, powerfully strengthens the hypothesis that BPA is a significant environmental diabetogen.[12]

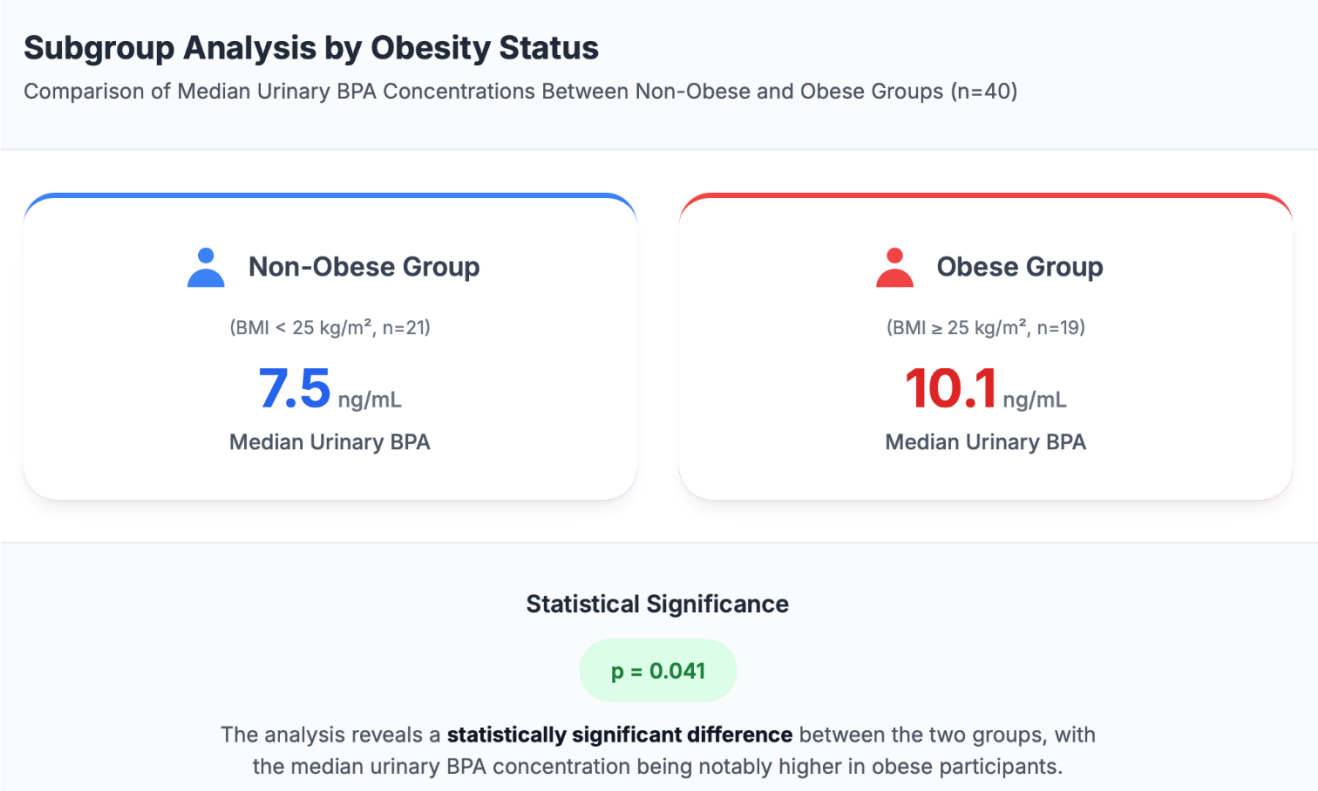

Figure 4. Subgroup analysis by obesity status.

The independent positive association between urinary BPA and HOMA-IR (β = 0.58), a cornerstone of our findings, aligns with and extends a large body of previous research. Our use of multivariable analysis, however, adds a crucial layer of evidence, suggesting that this link is not merely an artifact of confounding by adiposity. The pathophysiological mechanisms underpinning this association are deeply rooted in cellular biology. Experimental data have conclusively shown that BPA can directly antagonize the insulin signaling cascade. A key mechanism involves the upregulation of Suppressor of Cytokine Signaling 3 (SOCS-3). BPA exposure promotes the expression of SOCS-3, a protein that acts as a potent negative regulator of insulin action by binding directly to the insulin receptor (IR) and its primary downstream substrate, Insulin Receptor Substrate-1 (IRS-1).[13] This binding sterically hinders the tyrosine phosphorylation of IR and IRS-1, effectively blocking the propagation of the signal down the PI3K/Akt pathway, which is essential for glucose uptake and metabolism. This molecular sabotage induces a state of cellular insulin resistance. Furthermore, BPA acts as an obesogen, promoting adipogenesis and altering the secretome of adipose tissue.[14] It shifts adipose tissue towards a pro-inflammatory phenotype,

increasing the release of adipokines like TNF-α and IL-6. These circulating inflammatory cytokines are known systemic inducers of insulin resistance in the liver and muscle tissue. Our subgroup analysis, which found significantly higher BPA levels in obese participants, supports this adipocentric mechanism, suggesting that BPA contributes to insulin resistance both through direct cellular interference and indirectly via its effects on adipose tissue mass and inflammatory function. The regression model shows, however, that even when BMI is accounted for, BPA retains its strong independent association with HOMA-IR.[15]

The most novel and arguably most important finding of this study is the powerful, independent inverse association between urinary BPA and β-cell function, an effect that is dramatically magnified during a metabolic challenge. While the adjusted negative association with the fasting C-peptide index was statistically significant (β = -0.45), the substantially stronger and more profound association with the 1-hour post-OGTT C-peptide index (β = -0.79) is of immense clinical and biological significance. This finding provides strong evidence that the most deleterious metabolic impact of BPA is not on the β-cell's baseline, housekeeping secretion, but on its crucial ability to mount a robust and adequate insulin response to a glycemic load.[16] This failure of stimulated secretion, or "β-cell exhaustion," represents the critical tipping point in the natural history of T2DM. A healthy pancreas can often compensate for years of underlying insulin resistance through hypersecretion; it is the ultimate loss of this compensatory capacity that leads to decompensation and overt hyperglycemia. Our data, demonstrating an independent association that explains a large proportion of the variance in stimulated function (R2=0.69 for the full model), strongly finger BPA exposure as a significant environmental correlate of this functional failure.

The molecular mechanisms driving this potent BPA-induced β-cell toxicity are multifaceted but appear to converge on the induction of overwhelming cellular stress. Pancreatic β-cells are rich in receptors that BPA can target, including classical estrogen receptors (ERα, ERβ) and the G protein-coupled estrogen receptor (GPER1).[17] Chronic, inappropriate agonism of these receptors by BPA, an environmental xenoestrogen, disrupts the tightly regulated intracellular calcium (Ca^{2+}) oscillations that are fundamental to the process of glucose-stimulated insulin secretion. More critically, this dysregulation, combined with other insults, can lead to a build-up of misfolded proinsulin molecules within the endoplasmic reticulum (ER), triggering a state of severe ER stress. Protracted ER stress activates a cellular program called the unfolded protein response (UPR).[18] While initially adaptive, a persistent UPR, unable to restore homeostasis, pivots towards initiating pro-apoptotic pathways (such as the CHOP and JNK pathways), leading directly to β-cell death. Concurrently, BPA has been shown to directly impair mitochondrial function and increase the production of reactive oxygen species (ROS) within β-cells. This overwhelms the β-cell's relatively weak intrinsic antioxidant defenses, leading to a state of oxidative stress, which further damages critical cellular components like DNA, lipids, and proteins—including those essential for insulin synthesis and the secretory machinery. The remarkably strong, independent negative association we observed with the 1h-CPI suggests that BPA acts as a powerful inhibitor of this dynamic, energy-intensive process of insulin synthesis, packaging, and exocytosis, which is a classic hallmark of β-cell glucotoxicity and failure.[18]

By demonstrating a robust, adjusted link to both insulin resistance and β-cell failure, our study frames BPA as a key environmental contributor to the vicious cycle of T2DM pathogenesis. On one hand, BPA exposure is independently associated with increased insulin resistance, which relentlessly increases the secretory demand placed on the pancreas. On the other hand, BPA is simultaneously associated with direct impairment and toxicity to the β-cells, critically reducing their capacity to meet this heightened demand.[19] This "dual-hit" mechanism, now supported

by multivariable-adjusted data, provides a compelling model for how a ubiquitous environmental chemical can significantly accelerate the progression of T2DM, pushing individuals from a state of compensated insulin resistance toward decompensated β-cell failure and overt disease.

These findings carry particular weight given the study's geographic context in Indonesia. Southeast Asia is a global hotspot for both the T2DM epidemic and rapid, often unregulated, industrialization, which invariably increases population-level exposure to chemicals like BPA. The strong effect sizes observed in our cohort suggest that such environmental exposures may be a more significant and underappreciated driver of the regional diabetes crisis than previously acknowledged. Our results provide crucial, locally-relevant evidence to a global dataset historically dominated by Western and East Asian cohorts, suggesting BPA's metabolic effects are a globally relevant phenomenon.[19]

The primary strength of this study is its use of multivariable regression analysis to move beyond simple correlation and establish independent associations, coupled with a robust sensitivity analysis that confirmed the findings. Further strengths include the use of the gold-standard LCMS method for BPA quantification and the comprehensive assessment of both insulin resistance and, critically, dynamic β-cell function. However, some limitations must be acknowledged. First, the cross-sectional design inherently precludes any inference of causality; we have demonstrated strong, independent associations, but cannot determine temporal sequence. The possibility of reverse causality—that advanced T2DM might alter BPA metabolism or excretion—while less likely, cannot be entirely dismissed without longitudinal data. Second, urinary BPA was measured from a single spot urine sample, which reflects recent exposure and is subject to intra-individual variability. While this is a common and accepted method in large-scale epidemiology, it may not perfectly represent long-term chronic exposure levels. Third, the consecutive sampling method, while pragmatic, is a non-probability technique and may be subject to selection bias, potentially limiting the generalizability of our findings beyond our specific clinic population. Finally, despite adjusting for major confounders, residual confounding from unmeasured factors such as detailed dietary patterns (which can be a source of both BPA and diabetogenic nutrients), physical activity levels, or co-exposure to other EDCs, cannot be fully ruled out.[20]

These compelling findings call for further investigation. Future research should prioritize longitudinal cohort studies in this population to establish temporality and confirm that higher BPA exposure precedes and predicts the decline in β-cell function. Mechanistic studies exploring gene-environment interactions and studies assessing the cumulative impact of exposure to a mixture of EDCs are also warranted.

5. Conclusion

In this cohort of Indonesian patients with T2DM, higher urinary BPA concentration is a significant and independent predictor of the dual pathophysiological hallmarks of the disease. After controlling for key confounders, BPA levels were strongly associated with greater insulin resistance and, more profoundly, with an inverse correlation with pancreatic β-cell functional reserve. This effect was most pronounced during a stimulated state, as measured by the 1-hour post-OGTT C-peptide index. These findings support the hypothesis that environmental BPA exposure acts as a significant metabolic disruptor, independently contributing to T2DM pathogenesis by impairing insulin sensitivity while simultaneously crippling the β-cell's ability to compensate. The powerful association with stimulated β-cell failure, in particular, highlights an urgent need for greater consideration of environmental factors in the clinical management and public health prevention strategies for T2DM, especially in rapidly industrializing and high-risk regions like Southeast Asia.

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