

## Original Article



## Ambient Fine Particulate Matter Exacerbates Ketogenesis in a Mouse Model of Type 2 Diabetes

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### Abstract

**Objective** Prior epidemiological research demonstrated an association between short-term exposure to fine particulate matter (PM<sub>2.5</sub>) and acute diabetic events, specifically diabetic ketoacidosis (DKA). However, mechanistic investigations remain lacking to substantiate biological link.

**Methods** Twenty 18-week-old male BKS db/db mice were randomly assigned to two groups ( $n = 10$  per group). Ambient PM<sub>2.5</sub> suspension (5 mg/kg in 50  $\mu$ L) or an equal volume of phosphate-buffered saline was intratracheally instilled once daily for three consecutive days. Within 24 hours after the final instillation (Day 3), serum  $\beta$ -hydroxybutyrate was quantified, and liver tissues were collected for transcriptomic profiling (RNA-seq) to explore potential mechanisms linking PM<sub>2.5</sub> to ketone body levels (i.e.,  $\beta$ -hydroxybutyrate).

**Results** The PM<sub>2.5</sub> group exhibited higher 3-hydroxybutyric acid levels than controls. The liver transcriptome differed significantly between groups. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses indicated differentially expressed genes were primarily associated with lipid metabolism. Further, 43 genes exhibited moderate-to-strong correlations with 3-hydroxybutyric acid (16 positive, 27 negative; coefficients 0.56 – 0.76). These genes are involved in fatty acid oxidation, lipogenesis, lipid transport, glucose metabolism, and inflammation.

**Conclusion** PM<sub>2.5</sub> exposure may enhance ketogenesis through disruption of hepatic glucolipid metabolism, providing mechanistic insight into its potential role in acute diabetic metabolic decompensation.

**Key words:** Fine particulate matter; Air pollution; Ketoacidosis; Biological mechanism

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### INTRODUCTION

Type 2 diabetes (T2D) represents a tremendous disease burden to humans worldwide<sup>[1]</sup>. Fine particulate matter (PM<sub>2.5</sub>, particulate matter with aerodynamic diameter of  $\leq 2.5 \mu\text{m}$ ) air pollution is a major risk

factor for cardiometabolic diseases<sup>[2-4]</sup>. A growing body of evidence indicates that short-term exposure to PM<sub>2.5</sub> is associated with an increased risk of diabetes morbidity and mortality<sup>[5-8]</sup>. Importantly, a nationwide, individual-level, case-crossover study reported that short-term exposure to PM<sub>2.5</sub> may precipitate death from T2D *via* exaggerating diabetic

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ketoacidosis (DKA), one of the major acute and fatal complications of diabetes<sup>[5]</sup>. Per interquartile range (IQR) increment in 3-day moving-average PM<sub>2.5</sub> concentrations were associated with 2.54% (1.04% – 4.06%) increase in DKA mortality<sup>[5]</sup>. Consistent with these finding, a time-series study in Chile also revealed positive associations of DKA hospitalizations with short-term PM<sub>2.5</sub> exposure, particularly among older populations<sup>[8]</sup>. Despite accumulating epidemiological evidence linking short-term PM<sub>2.5</sub> exposure to DKA, animal studies are still lacking to support the biological plausibility for this association.

Elevated circulating ketone bodies serve as a key biomarker for DAK. Ketone bodies mainly comprise acetoacetate,  $\beta$ -hydroxybutyrate, and acetone. Of these,  $\beta$ -hydroxybutyrate is the most abundant and stable circulating form, accounting for approximately 70–90% of total ketone bodies, and is therefore widely used as a biomarker of ketosis. It remains uncertain whether PM<sub>2.5</sub> exposure increases ketone body levels among diabetic individuals. Furthermore, as the central organ in regulating energy metabolism, the liver plays a vital role in fatty acid oxidation, ketone body production, and glucose homeostasis, making it a key target for studying metabolic disturbances related to diabetes. Previous epidemiological studies have indicated that PM<sub>2.5</sub> exposure is associated with an increased risk of chronic liver diseases<sup>[9,10]</sup>. Emerging toxicological evidence also suggests that PM<sub>2.5</sub> may impair hepatic glucose utilization by reducing tricarboxylic acid cycle capacity and may promote hepatic lipid dysregulation through enhancing de novo lipogenesis, altering phospholipid metabolism, and inhibiting fatty acid oxidation<sup>[11-13]</sup>. However, it has not been ascertained whether alterations in hepatic physiological activity mediate increases in ketone body levels following PM<sub>2.5</sub> exposure, especially in diabetic individuals. Transcriptome analysis is a powerful tool for understanding how environmental stimuli affect gene activity, and has been widely applied to discern early biological responses to air pollution exposure<sup>[14,15]</sup>. We have hypothesized that acute PM<sub>2.5</sub> exposure enhances ketogenesis in T2D by disrupting hepatic metabolism that can be detected by transcriptomic alterations in the liver.

## METHODS

### *Preparation of PM<sub>2.5</sub> Suspensions*

PM<sub>2.5</sub> was collected from the rooftop of Building

8 in the West Zone of Fenglin Campus, Fudan University (Shanghai, China) between December 2020 and February 2021, using quartz fiber filters. The average mass concentration of PM<sub>2.5</sub> during the sampling period was approximately 39  $\mu\text{g}/\text{m}^3$ . Prior to deployment, these filters underwent rigorous preparation procedures. In specific, the filters were baked in a furnace at 400 °C for 6 hours and then held in a chamber at 25 °C and 50% relative humidity for 24 hours. The conditioned filters were then installed on a TH-1000CII high-volume air particulate sampler equipped with a PM<sub>2.5</sub> cutter, with the sampling flow rate set at 1.05  $\text{m}^3/\text{min}$ . Samples were collected on each filter for 20 hours per day over three days. After sampling, the filters were reconditioned in the chamber for an additional 24 hours. The filters were then cut into pieces (approximately 1 × 3 cm), submerged in double-distilled water for 12 hours, and cleaned by ultrasonic vibration five times for 20 minutes each. The resulting liquid was filtered into a 50 mL centrifuge tube and centrifuged at 12,000 g for 20 minutes at 4 °C. The supernatant was discarded, leaving a small amount of liquid at the bottom of the tube. Particulate matter pelleted on tube walls was scraped into this liquid and resuspended. The PM<sub>2.5</sub> suspension was transferred to a hanging bottle, frozen at –80 °C for 12 hours, and then subjected to vacuum freeze-drying for 24 hours. The collected PM<sub>2.5</sub> samples were stored at –20 °C until further use.

### *Animal Experiment*

Our prior study that linked PM<sub>2.5</sub> to DKA mortality occurred in a population with T2D<sup>[5]</sup>, therefore the current study used seventeen-week-old male BKS db/db mice obtained from Finoc Biotech, Shanghai ( $n = 20$ ). Male mice were selected to minimize the potential confounding effects from fluctuating female sex hormones on lipid and glucose metabolism. The BKS db/db mouse is a well-established leptin receptor-deficient model that spontaneously develops T2D phenotypes, including hyperglycemia, hyperinsulinemia, and insulin resistance, thereby rendering it particularly suitable for investigating diabetes-related outcomes. All mice were acclimated for one week under controlled conditions (temperature: 20 ± 2 °C; relative humidity: 40%–70%) on a 12-h light/ dark cycle, with free access to standard chow and water. The protocols and the use of animals were approved by the Fudan University Animals Ethical and Uses Committee.

Mice were randomly assigned to receive intratracheal instillation of either PM<sub>2.5</sub> (5 mg/kg, collected from the aforementioned filters) suspended in 50  $\mu$ L phosphate-buffered saline (PBS; 0.01 M, pH7.4), or 50  $\mu$ L PBS alone (control). Toxicological studies have reported that exposure to 5 mg/kg induces metabolic disturbances and systemic inflammation in mice<sup>[16,17]</sup>. The PBS administered to the control group was prepared by extracting blank quartz filters. These blank filters underwent the exact same processing, sonication, and handling procedures as the PM<sub>2.5</sub>-laden filters. Exposures were performed once daily for three consecutive days, corresponding to the exposure window used in our previous human study<sup>[5]</sup>. Prior to administration, the suspension was sonicated for 20 minutes to reduce particle aggregation and vortexed for 30 seconds to ensure uniform dispersion. Mice were euthanized for blood and tissue collection within 24 hours from the final instillation (Day 3).

#### **Measurements of Circulating Ketone Bodies**

Blood was collected *via* eyeball enucleation, placed at room temperature for 1 hour, and centrifuged at 1000 g for 10 minutes at 4°C. The serum supernatant was then collected and stored at -80 °C until analyzed. Serum  $\beta$ -hydroxybutyrate levels were measured using the ketone body assay kit (Sigma-Aldrich, MAK134). Samples exhibiting severe hemolysis were excluded from the analysis of  $\beta$ -hydroxybutyrate, resulting in a final sample size of  $n = 9$  for the PBS group.

#### **Liver Tissue Harvest, RNA Isolation and Sequencing**

Liver tissue was harvested, flash frozen immediately and stored at -80°C until used for RNA isolation, sequencing and analysis. The transcriptomics assays include sample quality testing, library construction, library quality testing, and library sequencing. Specifically, liver RNA was extracted using TRIZOL (TRIZOL® Reagent, Invitrogen, USA). RNA quality and integrity were assessed by agarose gel electrophoresis, NanoPhotometer spectrophotometer, Qubit 2.0 Fluorometer, and Agilent 2100 Bioanalyzer. These analyses included determination of RNA integrity, DNA contamination, concentration, and purity (A260/A280 and A260/A230 ratios). Only samples with RNA Integrity Number (RIN)  $\geq 7$  were considered eligible for downstream analysis. Purified RNA was used to establish the RNA library using the Illumina TruSeq™ RNA Sample Prep Kit (Illumina, San Diego, CA, USA). Initially, seven mice were randomly selected from

each group for the analysis. The pre-defined quality criterion (RIN  $\geq 7$ ) resulted in one sample from the PM<sub>2.5</sub>-exposed to be excluded from analysis, leading to libraries from seven PBS-exposed and six PM<sub>2.5</sub>-exposed mice to be sequenced. All sequencing was performed with an Illumina Truseq SBS Kit (300cycles) on an Illumina NovaSeq 6000 platform. Raw reads were processed to remove low-quality reads and adapters. Clean reads were aligned to the mouse reference genome (GRCm39) using HISAT2 (v2.2.1). Gene-level read counts were quantified using featureCounts (v2.0.1). All samples were processed using the same experimental conditions to minimize batch variation. The mapping rates exceeding 95% for all samples, indicating high-quality sequencing data.

#### **Statistical Analysis**

Serum  $\beta$ -hydroxybutyrate levels were measured in 19 mice (PBS control group,  $n = 9$ ; PM<sub>2.5</sub>-exposed group,  $n = 10$ ). The normality of serum  $\beta$ -hydroxybutyrate levels was assessed using the Shapiro–Wilk test. Given that the data were not normally distributed, comparisons were performed using the Mann–Whitney U test. A two-sided  $P$ -value  $< 0.05$  was considered statistically significant. To strengthen the interpretation of the results beyond  $p$ -values, the Hodges–Lehmann estimate for the difference in location alongside 95% confidence intervals ( $CIs$ ) are reported. Additionally, the effect size ( $r$ ) was calculated ( $r = z/\sqrt{N}$ ) to quantify the magnitude of the observed effects (categorized as small  $< 0.3$ , moderate: 0.50–0.70, large  $\geq 0.70$ ).

Liver transcriptomic analysis was conducted in 13 mice (PM<sub>2.5</sub>-exposed group,  $n = 6$ ; PBS control group,  $n = 7$ ). Differentially expressed genes (DEGs) following PM<sub>2.5</sub> exposure were determined. Gene expression levels were initially represented by unnormalized raw counts, defined as the number of reads mapped to per gene. Genes were excluded if they had fewer than 10 raw counts or if counts per million (CPM) were  $< 1$  in more than half of the samples in each group<sup>[14]</sup>. After filtering, 11,842 genes were retained for downstream liver transcriptome analysis. Specifically, principal component analysis (PCA) was firstly conducted to assess within-group consistency and between-group separation based on the top 500 Variance Stabilizing Transformation-normalized genes with the highest variance. Differential expression analysis was performed using *DESeq2* (version: 1.48.2) based on raw counts<sup>[18]</sup>. To control for multiple testing,  $p$ -

values were adjusted using the Benjamini–Hochberg false discovery rate (FDR)<sup>[19]</sup>. Fold change (FC) between treatment and control groups was also calculated on a linear scale. Genes with  $FC > 1.50$  or  $< 0.66$  and  $FDR < 0.01$  were considered differentially expressed and visualized using volcano plots. Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed using the *clusterProfiler* package (version: 4.16.0) to identify biological significances. Finally, to identify potential candidate genes linking  $PM_{2.5}$  exposure to elevated ketone bodies, Spearman's rank correlation analysis between all DEGs ( $FC > 1.50$  or  $< 0.66$  and  $FDR < 0.01$ ) and serum  $\beta$ -hydroxybutyrate levels among the 13 mice were performed. To balance the risk of false positives with the retention of plausible biological signals in this analysis, an unadjusted  $P$ -value  $< 0.05$  threshold was applied for prioritization. Genes meeting this criterion were considered putative associations requiring further functional validation. All analyses were performed using *R* (version 4.5.1).

## RESULTS

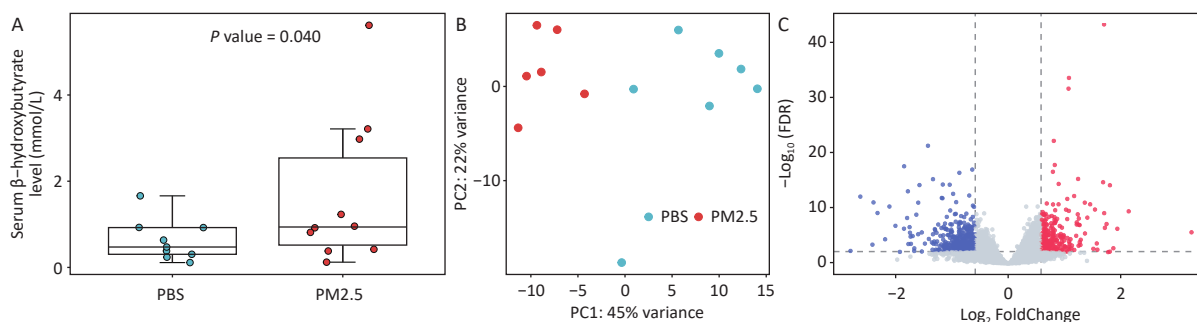
### Transcriptomic Alterations Following $PM_{2.5}$ Exposure

No significant differences in baseline body weight were observed between groups. Throughout the 3-day exposure period, all animals survived, and changes in body weight remained comparable between the  $PM_{2.5}$ -exposed and control groups ( $P > 0.05$ ; Supplementary Table S1). A significant

elevation in serum ketone body levels was seen in the  $PM_{2.5}$ -exposed group (median = 0.94 mmol/L; mean = 1.66 mmol/L) compared to the controls (median = 0.43 mmol/L; mean = 0.63 mmol/L) (Figure 1A). PCA further demonstrated distinct transcriptomic profiles between the two groups, with inter-group variation clearly exceeding intra-group variation (Figure 1B). Differential expression analysis identified 651 genes significantly altered following  $PM_{2.5}$  exposure, including 234 upregulated and 417 downregulated genes (Figure 1C). A complete list of these DEGs is provided in Supplementary Table S2.

### Pathways in Relation to $PM_{2.5}$ Exposure

A total of 573 GO terms were significantly enriched following  $PM_{2.5}$  exposure, including 481 biological processes, 70 molecular functions, and 22 cellular components (Supplementary Table S3). For biological processes, the top 20 enriched terms indicated that DEGs were largely related to lipid metabolism and inflammatory immune responses. Affected pathways included fatty acid metabolism, carboxylic acid biosynthesis, organic acid biosynthesis, steroid metabolism, monocarboxylic acid biosynthesis, and fatty acid biosynthesis (Table 1). The top 20 terms of molecular function were mostly related to energy metabolism and redox activity, such as oxidoreductase activity, monooxygenase activity, heme binding, and sulfur compound binding (Table 2). For cellular components, the top 20 enriched terms were primarily related to membrane and organelle structures, including endoplasmic reticulum membrane, intrinsic and integral component of



**Figure 1.** Effect of  $PM_{2.5}$  exposure on serum ketone bodies and liver transcriptome. (A) Circulating ketone bodies,  $n = 9$  or  $10$  per group; (B) Principal component analysis for liver transcriptome. Red circles refer to mice in  $PM_{2.5}$  group, and blue circles refer to mice in PBS group.  $n = 6-7$  per group; (C) Volcano plot for the liver transcriptome following  $PM_{2.5}$  exposure. Red, blue, and gray circles refer to up-regulated ( $FDR < 0.01$  & fold change  $> 1.5$ ), down-regulated ( $FDR < 0.01$  & fold change  $< 2/3$ ), and unchanged genes, respectively, after  $PM_{2.5}$  exposure. PBS, phosphate-buffered saline;  $PM_{2.5}$ , fine particulate matter; FDR, false discovery rate.

endoplasmic reticulum membrane, intrinsic and integral component of organelle membrane, protein-lipid complex, basement membrane and membrane raft (Table 3). KEGG pathway analysis identified 21 significantly enriched pathways, the majority were related to lipid synthesis and metabolism. These included fatty acid metabolism, steroid biosynthesis, biosynthesis of unsaturated fatty acids, and the peroxisome proliferators-activated receptors (*PPAR*) signaling pathway (Table 4).

#### **Correlations between DEGs and Serum $\beta$ -hydroxybutyrate**

We identified 43 DEGs that significantly correlated with serum  $\beta$ -hydroxybutyrate level, including 16 with positive and 27 with negative correlations (Figure 2). The absolute correlation coefficients ranged from 0.56 to 0.76, indicating moderate to strong associations (Figure 2; Table 5). As summarized in Table 5, these genes were primarily involved in lipid and carbohydrate

metabolism, insulin resistance, inflammation, and immune response (Supplementary Table S3; Table 4).

## **DISCUSSION**

This study supports previous epidemiological findings linking short-term  $PM_{2.5}$  exposure to DKA. We observed significantly elevated serum ketone bodies in T2D mice following  $PM_{2.5}$  exposure. Transcriptomic profiling of liver tissue revealed substantial alterations in gene expression induced by  $PM_{2.5}$ . Importantly, a subset of these DEGs, particularly those involved in glycolipid metabolism, showed significant correlations with serum ketone body levels. Together, these findings support the hypothesis that acute  $PM_{2.5}$  exposure exacerbates diabetes and drives ketogenesis through disruption of hepatic glycolipid metabolic processes.

Although more studies have shown exacerbated diabetes in association with acute exposure to  $PM_{2.5}$ ,

**Table 1.** Top 20 pathways of biological processes enriched by the differentially expressed genes following  $PM_{2.5}$  exposure

ID	Biological processes	FDR	Count
GO:0006631	Fatty acid metabolic process	< 0.001	51
GO:0046394	Carboxylic acid biosynthetic process	< 0.001	37
GO:0016053	Organic acid biosynthetic process	< 0.001	37
GO:0008202	Steroid metabolic process	< 0.001	40
GO:0072330	Monocarboxylic acid biosynthetic process	< 0.001	30
GO:0032103	Positive regulation of response to external stimulus	< 0.001	38
GO:0006633	Fatty acid biosynthetic process	< 0.001	21
GO:1901617	Organic hydroxy compound biosynthetic process	< 0.001	26
GO:0006695	Cholesterol biosynthetic process	< 0.001	13
GO:1902653	Secondary alcohol biosynthetic process	< 0.001	13
GO:0006066	Alcohol metabolic process	< 0.001	32
GO:0001676	Long-chain fatty acid metabolic process	< 0.001	18
GO:0006694	Steroid biosynthetic process	< 0.001	21
GO:0016126	Sterol biosynthetic process	< 0.001	13
GO:1902652	Secondary alcohol metabolic process	< 0.001	20
GO:0006790	Sulfur compound metabolic process	< 0.001	30
GO:0042060	Wound healing	< 0.001	32
GO:0120254	Olefinic compound metabolic process	< 0.001	20
GO:0046889	Positive regulation of lipid biosynthetic process	< 0.001	16
GO:0046890	Regulation of lipid biosynthetic process	< 0.001	22

**Note.** FDR < 0.05 were considered statistically significant. GO, Gene Ontology;  $PM_{2.5}$ , fine particulate matter; FDR, false discovery rate.

animal models supporting these findings have been limited. Previous studies on mechanism of action have focused on the chronic effects of PM<sub>2.5</sub> on glucose metabolism. For example, Rajagopalan et al.<sup>[20]</sup> reported that long-term exposure of C57BL/6J mice to high concentrations of PM<sub>2.5</sub> for 14 weeks impaired glucose tolerance and insulin sensitivity, accompanied by marked transcriptomic alterations in liver, adipose, and muscle tissues. Similarly, Liu et al.<sup>[21]</sup> found that diabetic mice exposed to PM<sub>2.5</sub> for 4–8 weeks exhibited disrupted energy metabolism, reduced insulin sensitivity, and impaired glucose tolerance, with activation of inhibitor of nuclear factor kappa-B kinase subunit beta (IKK- $\beta$ ) as a potential cause. A few epidemiological and toxicological studies have reported the acute effects of air pollution on glucose metabolism with inconsistent results<sup>[22-24]</sup>. For

example, several panel studies reported that short-term exposure to PM<sub>2.5</sub> is associated with imbalances in glucose and insulin homeostasis<sup>[22,23]</sup>. Whereas, a toxicological study reported no changes in blood glucose levels following acute exposure to PM<sub>2.5</sub><sup>[24]</sup>. Importantly, the acute exacerbation of diabetes is often driven by the development of severe complications, rather than merely fluctuations in blood glucose. Therefore, it is essential to investigate the mechanisms by which PM<sub>2.5</sub> exposure may affect acute diabetic complications, such as DKA. This exploration is crucial for establishing a biological rationale underlying how short-term PM<sub>2.5</sub> exposure leads to the acute deterioration of diabetes.

Currently, limited studies have investigated the associations between air pollution and ketone bodies<sup>[25,26]</sup>. In diabetic mouse models, circulating  $\beta$ -

**Table 2.** Top 20 pathways of molecular function enriched by the differentially expressed genes following PM<sub>2.5</sub> exposure

ID	Molecular function	FDR	Count
GO:0016705	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	< 0.001	31
GO:0016717	Oxidoreductase activity, acting on paired donors, with Oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water	< 0.001	8
GO:0004497	Monooxygenase activity	< 0.001	21
GO:0020037	Heme binding	< 0.001	19
GO:1901681	Sulfur compound binding	< 0.001	26
GO:0046906	Tetrapyrrole binding	< 0.001	19
GO:0005506	Iron ion binding	< 0.001	19
GO:0008395	Steroid hydroxylase activity	< 0.001	11
GO:0016712	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen	< 0.001	11
GO:0016709	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen	< 0.001	10
GO:0101021	Estrogen 2-hydroxylase activity	0.002	5
GO:0030246	Carbohydrate binding	0.002	21
GO:0005496	Steroid binding	0.002	13
GO:0048029	Monosaccharide binding	0.002	11
GO:0005201	Extracellular matrix structural constituent	0.003	14
GO:0033218	Amide binding	0.004	27
GO:0043295	Glutathione binding	0.004	5
GO:0070643	Vitamin D 25-hydroxylase activity	0.004	4
GO:1900750	Oligopeptide binding	0.005	5
GO:0052689	Carboxylic ester hydrolase activity	0.005	14

**Note.** FDR < 0.05 were considered statistically significant. GO, Gene Ontology; PM<sub>2.5</sub>, fine particulate matter; FDR, false discovery rate.

hydroxybutyrate levels are typically below 1.0 mmol/L under physiological conditions. In our study, PM<sub>2.5</sub> exposure induced a pronounced right-skewed increase in  $\beta$ -hydroxybutyrate levels (median: 0.90 mmol/L; mean: 1.66 mmol/L), indicating that a subset of diabetic mice developed ketosis approaching metabolic decompensation following exposure. In contrast, the control group remained metabolically stable (median: 0.52 mmol/L; mean: 0.63 mmol/L). These results align with earlier findings in wild-type mice, where PM<sub>2.5</sub> exposure elevated ketone body levels in serum<sup>[26]</sup> and in cardiac tissue<sup>[27]</sup>, particularly after exposure to water-soluble PM<sub>2.5</sub> components<sup>[26]</sup>. Conversely, another study reported reduced hepatic ketone bodies following intratracheal exposure to PM<sub>2.5</sub><sup>[25]</sup>. These discrepancies may be related to differences in mouse model backgrounds, exposure route, or PM<sub>2.5</sub> components. Furthermore, our study identified a number of genes that may play a significant role in PM<sub>2.5</sub>-induced ketogenesis, most of which are

involved in carbohydrate and lipid metabolism, inflammatory responses, and related biological processes.

This study reports that PM<sub>2.5</sub> exposure altered lipid metabolism pathways, particularly by shifting the hepatic balance toward fatty acid mobilization and mitochondrial  $\beta$ -oxidation. Enhanced breakdown of hepatic- and phosphor-lipids provide an abundant supply of free fatty acids (FFAs), which serve as the primary substrates for ketone body production. The upregulation of mitochondrial  $\beta$ -oxidation pathways also accelerates the conversion of these FFAs into acetyl-CoA, the direct precursor for ketogenesis. These findings contrast with other recent evidence suggesting that short-term PM<sub>2.5</sub> exposure may inhibit lipolysis and fatty acid oxidation in the livers of wild-type mice<sup>[28]</sup>. That evidence indicated that increased lipolysis and fatty acid oxidation occur only after long-term exposure, possibly as an adaptive response<sup>[28]</sup>. Of note, we observed such enhancement even after short-term

**Table 3.** Top 20 pathways of cell composition enriched by the differentially expressed genes following PM<sub>2.5</sub> exposure

ID	Cell composition	FDR	Count
GO:0062023	Collagen-containing extracellular matrix	0.001	29
GO:0031227	Intrinsic component of endoplasmic reticulum membrane	0.009	15
GO:0030176	Integral component of endoplasmic reticulum membrane	0.013	14
GO:0031301	Integral component of organelle membrane	0.014	24
GO:0031300	Intrinsic component of organelle membrane	0.014	25
GO:0005583	Fibrillar collagen trimer	0.014	4
GO:0098643	Banded collagen fibril	0.014	4
GO:0032994	Protein-lipid complex	0.022	7
GO:0005604	Basement membrane	0.023	11
GO:0045121	Membrane raft	0.025	23
GO:0098857	Membrane microdomain	0.025	23
GO:0033116	Endoplasmic reticulum-Golgi intermediate Compartment membrane	0.025	4
GO:0022626	Cytosolic ribosome	0.025	10
GO:0005777	Peroxisome	0.025	12
GO:0042579	Microbody	0.025	12
GO:0045171	Intercellular bridge	0.040	9
GO:0034358	Plasma lipoprotein particle	0.040	6
GO:1990777	Lipoprotein particle	0.040	6
GO:0009925	Basal plasma membrane	0.040	17
GO:0098644	Complex of collagen trimers	0.040	4

**Note.** FDR < 0.05 were considered statistically significant. GO, Gene Ontology; PM2.5, fine particulate matter; FDR, false discovery rate.

exposure in our study. This discrepancy may be attributable to differences in mouse models, route of exposure or PM<sub>2.5</sub> composition. Although the exact molecular mediators require further validation, transcriptomic data reported here highlights several candidate genes that warrant further study through targeted mechanistic approaches. For instance, the upregulation of hydroxysteroid (17-beta) dehydrogenase 10 (*Hsd17b10*) and cytochrome P450, family 2, subfamily j, polypeptide 9 (*Cyp2j9*) could potentially facilitate mitochondrial fatty acid  $\beta$ -oxidation<sup>[29,30]</sup>.

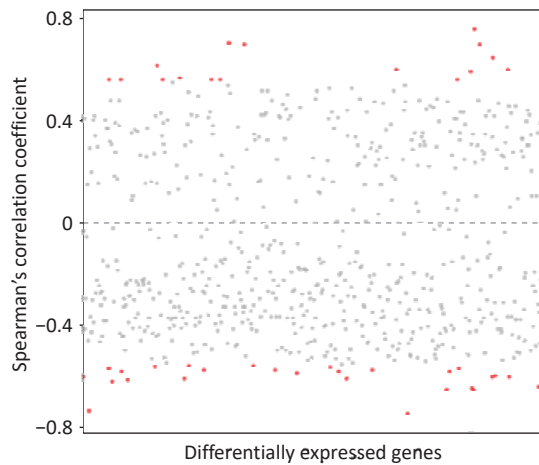
Beyond lipid oxidation, pathways involved in intra- and intercellular lipid transport may also play a role in regulating ketogenesis<sup>[31]</sup>, as suggested by altered gene expression we identified that link PM<sub>2.5</sub> exposure to elevated ketone body levels. For example, Mid1 interacting protein 1 (*Mid1ip1*), an upstream regulator of acetyl-CoA carboxylase (*ACC*), normally promotes fatty acid carboxylation, thereby restricting entry into mitochondria  $\beta$ -oxidation<sup>[32]</sup>. We observed that PM<sub>2.5</sub> exposure suppressed

*Mid1ip1* expression that also negatively correlated with ketone body levels, suggesting reduced *Mid1ip1* may lower *ACC* activity and subsequently facilitate mitochondrial fatty acid  $\beta$ -oxidation, ultimately enhancing ketone body production. Also found were genes related to glucose metabolism and insulin function that may mediate the relationship between PM<sub>2.5</sub> and ketogenesis, such as one cut domain, family member 1 (*Onecut1*), cytochrome P450, family 2, subfamily d, polypeptide 40 (*Cyp2d40*) and glutathione S-transferase, mu 6 (*Gstm6*)<sup>[33-35]</sup>. Normally, hepatic insulin signaling promotes glycolysis and lipogenesis. When signaling is impaired following PM<sub>2.5</sub> exposure<sup>[36,37]</sup>, normal energy pathways are compromised, and fatty acid oxidation is accelerated as an alternative energy source, leading to increased ketone body production. Inflammation is also reported to exacerbate localized insulin resistance and disrupt glucose metabolism<sup>[38]</sup>. Here the finding that PM<sub>2.5</sub> exposure appears to activate inflammatory cascades, as suggested by DEGs such as histidine

**Table 4.** Top 20 KEGG pathways enriched by the differentially expressed genes following PM<sub>2.5</sub> exposure

ID	KEGG pathways	FDR	Count
mmu00100	Steroid biosynthesis	< 0.001	8
mmu01040	Biosynthesis of unsaturated fatty acids	< 0.001	9
mmu03320	PPAR signaling pathway	< 0.001	14
mmu00480	Glutathione metabolism	0.004	11
mmu04979	Cholesterol metabolism	0.004	9
mmu01212	Fatty acid metabolism	0.004	10
mmu00983	Drug metabolism - other enzymes	0.004	12
mmu05417	Lipid and atherosclerosis	0.005	20
mmu01524	Platinum drug resistance	0.005	11
mmu00830	Retinol metabolism	0.006	12
mmu05204	Chemical carcinogenesis - DNA adducts	0.006	11
mmu00982	Drug metabolism - cytochrome P450	0.006	10
mmu05418	Fluid shear stress and atherosclerosis	0.007	15
mmu00061	Fatty acid biosynthesis	0.01	5
mmu04115	p53 signaling pathway	0.025	9
mmu00980	Metabolism of xenobiotics by cytochrome P450	0.026	9
mmu05207	Chemical carcinogenesis - receptor activation	0.028	18
mmu04650	Natural killer cell mediated cytotoxicity	0.028	12
mmu04936	Alcoholic liver disease	0.029	13
mmu00591	Linoleic acid metabolism	0.029	7

Note. FDR < 0.05 were considered statistically significant. KEGG, Kyoto Encyclopedia of Genes and Genomes; PM<sub>2.5</sub>, fine particulate matter; FDR, false discovery rate.



**Figure 2.** The Spearman's correlation between serum ketone bodies and differentially expressed genes. Each dot represents a differentially expressed genes, with red indicating statistically significant correlation between ( $P < 0.05$ ) serum ketone bodies and differentially expressed genes, and gray indicating non-significant correlation.

decarboxylase (*Hdc*) and ATPase family, AAA domain containing 2 (*Atad2*)<sup>[39,40]</sup>, alongside with targets like lectin, mannose-binding 2-like (*Lman2l*), opsin 3 (*Opn3*), zinc finger protein 599 (*Zfp599*), and SH2 domain containing 4A (*Sh2d4a*), whose roles in metabolism remain to be fully elucidated, suggests further study is needed.

It is important to note that ketosis is a multi-organ metabolic disruption. While our transcriptomic analysis focused on the liver as the primary site of ketogenesis,  $PM_{2.5}$  exposure likely exerts systemic effects. For instance, systemic inflammation induced by  $PM_{2.5}$  may exacerbate insulin resistance and trigger lipolysis in adipose tissue, releasing excessive FFAs into the circulation to serve as substrates for hepatic ketogenesis<sup>[41]</sup>. Additionally,  $PM_{2.5}$  might impair the utilization of ketone bodies in peripheral tissues, such as skeletal muscle<sup>[42]</sup>. Future studies analyzing multi-organ transcriptomics are needed to fully elucidate the systemic mechanisms mediating  $PM_{2.5}$ -induced ketosis.

The major strength of this study is that it

**Table 5.** Details of differentially expressed genes that significantly altered by  $PM_{2.5}$  exposure and associated with serum ketone bodies

ID	Gene name	Chang following $PM_{2.5}$ exposure	$r^*$	P value
Lipid metabolism				
ENSMUSG00000060675	Plaat3	Up	0.76	0.004
ENSMUSG00000060131	Atp8b4	Down	-0.65	0.020
ENSMUSG00000008035	Mid1ip1	Down	-0.62	0.027
ENSMUSG00000020776	Fbf1	Up	0.62	0.029
ENSMUSG00000029553	Tfec	Down	-0.58	0.043
ENSMUSG00000056220	Pla2g4a	Down	-0.57	0.045
ENSMUSG00000022092	Ppp3cc	Up	0.57	0.047
ENSMUSG00000022816	Fstl1	Down	-0.56	0.050
ENSMUSG00000021135	Slc10a1	Up	0.56	0.050
ENSMUSG00000025260	Hsd17b10	Up	0.56	0.050
ENSMUSG00000015224	Cyp2j9	Up	0.56	0.050
Glucose metabolism and insulin resistance				
ENSMUSG00000043013	Onecut1	Down	-0.75	0.005
ENSMUSG00000016494	Cd34	Down	-0.62	0.029
ENSMUSG00000068083	Cyp2d40	Down	-0.6	0.032
ENSMUSG00000000058	Cav2	Down	-0.6	0.032
ENSMUSG00000068762	Gstm6	Down	-0.6	0.034
ENSMUSG00000034785	Dio1	Down	-0.58	0.040
ENSMUSG00000039005	Tlr4	Down	-0.58	0.043

					Continued
ID	Gene name	Chang following PM <sub>2.5</sub> exposure	<i>r</i> <sup>*</sup>	<i>P</i> value	
Inflammation					
ENSMUSG00000027360	Hdc	Up	0.70	0.010	
ENSMUSG00000060441	Trim5	Down	-0.65	0.018	
ENSMUSG00000022360	Atad2	Down	-0.61	0.030	
ENSMUSG00000059970	Hspa2	Up	0.59	0.033	
ENSMUSG00000028037	Ifi44	Down	-0.56	0.050	
ENSMUSG00000056054	S100a8	Up	0.56	0.050	
Others					
ENSMUSG00000001143	Lman2l	Down	-0.74	0.006	
ENSMUSG00000026525	Opn3	Up	0.70	0.010	
ENSMUSG00000062794	Zfp599	Up	0.70	0.010	
ENSMUSG00000053886	Sh2d4a	Down	-0.65	0.018	
ENSMUSG00000068101	Cenpm	Up	0.65	0.020	
ENSMUSG00000105096	Gbp10	Down	-0.64	0.021	
ENSMUSG00000035910	Dcdc2a	Down	-0.61	0.030	
ENSMUSG00000073678	Pgap1	Down	-0.60	0.032	
ENSMUSG00000040767	Snrnp25	Up	0.60	0.034	
ENSMUSG00000072964	Bhlhb9	Up	0.60	0.034	
ENSMUSG00000030956	Fam53b	Down	-0.59	0.038	
ENSMUSG00000015340	Cybb	Down	-0.58	0.040	
ENSMUSG00000054404	Slfn5	Down	-0.58	0.040	
ENSMUSG00000024691	Fam111a	Down	-0.58	0.043	
ENSMUSG00000020681	Ace	Down	-0.56	0.045	
ENSMUSG00000006219	Fblim1	Down	-0.57	0.045	
ENSMUSG00000033792	Atp7a	Down	-0.57	0.047	
ENSMUSG00000006241	Ccdc159	Up	0.56	0.050	
ENSMUSG00000026035	Ppil3	Up	0.56	0.050	

**Note.** *P* values < 0.05 were considered statistically significant. <sup>\*</sup> the correlation coefficients between ketone bodies and differentially expressed genes. PM<sub>2.5</sub>, fine particulate matter.

provides biological plausibility for the association between short-term PM<sub>2.5</sub> exposure and acute exacerbation of diabetes. The non-targeted transcriptomic profiling further yielded valuable insights for future mechanistic investigations. Nevertheless, several limitations should be noted. First, PM<sub>2.5</sub> exposure was administered *via* intratracheal instillation rather than in an inhalation chamber. Although intratracheal exposure is widely used in short-term toxicology studies, it does not fully replicate the natural inhalation process, and replication using inhalation chambers is warranted. Second, the effects of PM<sub>2.5</sub> may vary depending on composition. For example, water-soluble PM<sub>2.5</sub>

components, rather than insoluble components, were found to increase serum ketone body levels in wild-type mice<sup>[26]</sup>; Liu et al.<sup>[43]</sup> revealed that exposure to PM<sub>2.5</sub> enriched with metals such as Mn, Cu, and Ni may cause significant hepatic mitochondrial damage. In the present study, the effects of individual PM<sub>2.5</sub> components on ketogenesis were not characterized due to lack of relevant data. Therefore, the generalizability of our findings to PM<sub>2.5</sub> from other regions or sources should be interpreted with caution. Third, while our study observed significantly elevated serum  $\beta$ -hydroxybutyrate levels indicating ketosis, we did not evaluate blood pH or bicarbonate levels. Clinically, DKA is defined by the triad of

hyperglycemia, ketosis, and metabolic acidosis. Therefore, current findings primarily demonstrate that PM<sub>2.5</sub> exacerbates ketosis, rather than confirming the development of DKA. Future studies incorporating comprehensive blood gas analyses are needed to confirm the occurrence of metabolic acidosis. Fourth, only male mice were used to minimize confounding variance from estrous cycle fluctuations. Future investigations should include both sexes to elucidate any sex-specific effects of PM<sub>2.5</sub> on ketone body metabolism. Fifth, the present investigation relied on transcriptomic data using RNA sequencing that provides valuable insights into pathway alterations, the functional consequences of the observed gene expression changes require further validation at the protein and functional levels. Finally, the mouse model used here exhibits profound dysregulation of glycolipid metabolism, which may limit the generalizability of the observed metabolic abnormalities following PM<sub>2.5</sub> exposure. However, this model was deliberately chosen to mimic advanced diabetes and thus fits the objective of testing whether PM<sub>2.5</sub> exacerbates the disease. Moreover, the only difference between exposed and control groups was PM<sub>2.5</sub> exposure, making it reasonable to attribute the observed differences to this exposure.

In conclusion, building on prior epidemiological evidence, we demonstrated that short-term exposure to PM<sub>2.5</sub> may precipitate ketogenesis in diabetic individuals by altering hepatic transcriptomic profiles related to fatty acid oxidation, lipogenesis, lipid transport, glucose metabolism, and inflammation. Our study provides novel experimental evidence supporting the biological plausibility of the link between acute PM<sub>2.5</sub> exposure and exacerbation of diabetes, highlighting potential molecular pathways through which air pollution can acutely aggravate disease. Nevertheless, further targeted and mechanistic investigations are warranted to validate and extend these preliminary observations. Clinical samples from T2D patients are needed to confirm these molecular pathways in humans.

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**Authors' Contributions** Conceived and designed the study, acquired funding and revised the manuscript:

Renjie Chen; Performed the experiments, investigation, formal analysis, and drafted the original manuscript: Huihuan Luo and Yuanting Xie; All authors reviewed and edited the manuscript. All authors had full access to all the data in the study. All authors have final responsibility for the decision to submit for publication.

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