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Review

Volatilomics insights in older adults with diabetes: from metabolic mechanisms to precision geriatric medicine

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ABSTRACT

Aims: This review aims to evaluate the hypothesis that Volatilomics-the comprehensive analysis of volatile organic compounds (VOCs) from breath, skin, urine, and other biological matrices-can serve as a non-invasive tool to characterize metabolic alterations associated with aging and diabetes mellitus in older adults, supporting precision geriatric medicine.

Methods: We conducted a narrative review of experimental and clinical studies investigating VOC signatures in aging individuals with diabetes. The analysis focused on associations between VOC profiles and key biological mechanisms, including oxidative stress, lipid peroxidation, mitochondrial dysfunction, inflammaging, and host–microbiome interactions. We also examined analytical technologies and methodologies, such as advanced mass spectrometry platforms, sensor-based devices, and artificial intelligence-driven pattern recognition approaches.

Results: The reviewed evidence suggests that diabetes is associated with distinctive VOC patterns; however, direct evidence specifically derived from geriatric cohorts remains limited. These VOC patterns are associated with glycemic imbalance and age-related metabolic dysfunction and show potential utility for early detection, clinical phenotyping, and individualized monitoring, particularly in frail or multimorbid patients. Technological advances are facilitating translation toward portable and home-based applications.

Conclusions: Volatilomics represents a promising, non-invasive approach to improve diabetes management in aging populations. Despite its potential, challenges remain, including methodological heterogeneity, limited reproducibility, confounding effects of comorbidities and polypharmacy, and the lack of large longitudinal geriatric cohorts.

Abbreviations: ACE, Angiotensin-Converting Enzyme; AI, Artificial Intelligence; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; e-nose, Electronic Nose; FeNO, Fractional Exhaled Nitric Oxide; GC–MS, Gas Chromatography-Mass Spectrometry; HbA1c, Glycated Hemoglobin; HF, Heart Failure; IMS, Ion Mobility Spectrometry; MOS, Metal Oxide Semiconductor; MS, Mass Spectrometry; PTR–MS, Proton Transfer Reaction–Mass Spectrometry; RBC, Red Blood Cells; SCFAs, Short-Chain Fatty Acids; SIFT–MS, Selected Ion Flow Tube–Mass Spectrometry; T1D, Type 1 Diabetes; T2DM, Type 2 Diabetes Mellitus; VOCs, Volatile Organic Compounds.

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1. Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic conditions in older adults, deeply interwoven with the biological processes of aging.[1] Globally, the number of individuals over the age of 65 living with diabetes is increasing rapidly, reflecting both the demographic shift toward aging societies and the strong age-dependence of type 2 diabetes mellitus (T2DM). [2]. With advancing age, the incidence of T2DM and its complications rises steeply, contributing significantly to frailty, disability, and mortality [3]. Beyond its prevalence, diabetes profoundly influences the quality of life and functional independence of older adults. [3]. The aging organism undergoes profound metabolic, immunological, and physiological changes that modulate the onset and progression of diabetes [4]. These include mitochondrial dysfunction, chronic low-grade inflammation ("inflammaging"), sarcopenia, altered insulin sensitivity, and shifts in the gut microbiome [5]. Each of these processes can contribute not only to the development of diabetes but also to the heterogeneity of its clinical presentation in older individuals [6]. Conversely, diabetes itself acts as a biological accelerator of aging, exacerbating oxidative stress, endothelial dysfunction, vascular damage [7]. This bidirectional interaction creates a vicious cycle in which aging promotes diabetes, and diabetes amplifies age-related decline, ultimately increasing the burden of multimorbidity and complicating clinical management in geriatric populations [8]. Traditional diagnostic and monitoring strategies for diabetes—such as fasting plasma glucose, hemoglobin A1c (HbA1c), and continuous glucose monitoring (CGM) remain the mainstay of care but have important limitations in older adults[9,10]. Invasiveness and age-related comorbidities, including renal or hepatic dysfunction and anemia-related changes in red blood cell turnover, may reduce feasibility and biomarker accuracy, particularly for HbA1c interpretation [10]. This diversity demands a more nuanced and individualized approach to diagnosis and monitoring, aligned with the principles of precision geriatric medicine. [11] In this context, there is an urgent need for innovative diagnostic and monitoring tools that are non-invasive, accurate, and adaptable to the complexity of geriatric patients [12]. Among the emerging approaches, Volatilomics, the comprehensive study of VOCs released through breath, urine, skin, or other biological matrices, has attracted growing attention as a window into systemic metabolism [13]. VOCs are low-molecular-weight molecules generated by a wide range of physiological and pathological processes [14]. They mirror dynamic biochemical pathways such as oxidative stress, lipid peroxidation, amino acid catabolism, and host–microbiome interactions, all of which are profoundly altered in diabetes and aging [4]. Importantly, VOCs analysis provides a real-time snapshot of metabolic activity, capturing subtle fluctuations that may not be detectable with static blood-based biomarkers [15]. A growing body of evidence indicates that diabetes is associated with specific Volatilomics fingerprints [14]. However, most of these studies have been conducted in mixed-age cohorts, and age-specific volatilomic trajectories in older adults with diabetes remain insufficiently characterized. Exhaled acetone, a byproduct of ketone body metabolism, has been consistently reported to be elevated in person with diabetes and correlates with both glycemic status and ketosis [16]. Other compounds, including isoprene, ethanol, aldehydes, and sulfur-containing volatiles, have been linked to lipid metabolism, oxidative damage, and microbiome dysbiosis, reflecting the complex interplay between host metabolism and comorbid conditions [17]. Such profiles offer the potential to distinguish between different stages of disease, identify complications, and provide a non-invasive means of monitoring therapeutic response. Crucially, Volatilomics analysis aligns well with the principles of precision geriatric medicine [18]. Its non-invasive nature reduces the burden of testing in frail or multimorbid older adults, while its sensitivity to metabolic fluctuations offers opportunities for individualized monitoring and stratification [19]. Furthermore, the integration of Volatilomics with artificial intelligence and portable sensor technologies,such as electronic noses and machine learning (ML) classifiers, opens the door to bedside and home-based applications, bridging the gap between molecular diagnostics and patient-centered care in the aging population [20]. Despite these promising developments, the role of Volatilomics in the intersection between diabetes and aging remains largely unexplored [21]. Previous work has focused on identifying Volatilomics biomarkers of diabetes in general populations, but few efforts have systematically contextualized these findings within the biological processes of aging and the clinical complexity of geriatric medicine [22]. Unlike previous reviews that have mainly focused on VOC identification in general adult populations with diabetes or on technological aspects of breath analysis, the present review specifically integrates aging biology, geriatric multimorbidity, and volatilomic profiling within a precision medicine framework. To our knowledge, no prior review has systematically contextualized volatilomics within the clinical and biological complexity of older adults with diabetes while critically addressing methodological heterogeneity and translational gaps. Rather than advocating immediate clinical implementation, we define current evidence boundaries and propose a structured roadmap for future validation in geriatric diabetology (Graphical abstract).

2. Methods

This narrative review was conducted to synthesize current evidence on volatilomics in diabetes with specific attention to aging-related mechanisms and geriatric clinical complexity. A structured literature search was performed in PubMed/MEDLINE, Scopus, and Web of Science up to March 2025. Search terms included combinations of: "volatilomics", "volatile organic compounds", "VOCs", "breath analysis", "diabetes", "type 2 diabetes", "aging", "older adults", "frailty", "geriatric", "metabolomics", and "electronic nose". We included experimental, observational, proof-of-concept, and technology-oriented studies investigating VOC signatures in diabetes or aging populations. Reviews were considered when relevant to methodological or translational aspects. Studies exclusively focused on non-metabolic diseases without mechanistic relevance to diabetes or aging were excluded. Particular attention was given to study design, population characteristics (including age range), analytical platform, and reported limitations. Due to heterogeneity in methodologies and outcome measures, a quantitative *meta*-analysis was not feasible. Instead, findings were synthesized narratively, with emphasis on translational relevance and current evidence gaps. As this manuscript is a narrative review and does not include primary data analyses, no parametric, semiparametric, or nonparametric statistical models were directly implemented. Nevertheless, we recognize that rigorous selection of statistical methodologies is essential in primary volatilomic research, particularly considering the high dimensionality and potentially non-normal distribution of VOC datasets. Ensuring appropriate alignment between data characteristics and analytical strategies is crucial to prevent biased results and misleading interpretations.

Volatilomics: probing the metabolic signature of diabetes

Volatilomics represents a rapidly evolving frontier in biomedical research, offering a direct and non-invasive means of interrogating human metabolism through the analysis of VOCs [23]. VOCs arise from key biochemical pathways, mitochondrial function, oxidative stress, lipid peroxidation, amino-acid catabolism, and host–microbiome fermentation, and are released through breath, skin, urine, and related matrices, providing a dynamic fingerprint of systemic metabolism [24,25]. In diabetes mellitus, Volatilomics profiling has uncovered distinctive VOCs signatures that reflect underlying metabolic dysregulation and may inform diagnosis and monitoring in a non-invasive manner [26]. Although accumulating evidence supports associations between VOC profiles and metabolic dysregulation in diabetes, the strength, design, and geriatric representation of available studies vary considerably. To provide a structured overview of the current evidence base, Table 1 summarizes key investigations, including study design, sample size, population characteristics, analytical platforms, and major

Table 1
Summary of current evidence on volatilomics in diabetes and its relevance to older adults.

Study	Design	Population (Age)	N°	Matrix	Platform	Main VOC Findings	Clinical Association	Geriatric-Specific?	Key Limitations
Padberg et al., 2014	Case-control	T2DM adults (mixed age)	115	Plasma (metabolomics, volatile fraction)	GC–MS	Altered metabolic signature, including ketone-related VOCs	T2DM metabolic dysregulation	No	Not age-stratified
Tsunemi et al., 2022	Cross-sectional	Adults with diabetes	34	Breath	Semiconductor gas sensor	Exhaled acetone correlates with blood ketones	Glycemic and ketotic status	No	Small sample size
Yokokawa et al., 2017	Observational	HF patients with diabetes (older subgroup included)	102	Breath	Gas analysis	Elevated acetone in diabetic HF	HF severity and ketone metabolism	Partially	Strong comorbidity confounding
Wang & Wang, 2013	Historical review	Mixed-age	–	Breath	Multiple	Breath acetone consistently elevated in diabetes	Glycemic status	No	Narrative review
Swargiary et al., 2025	Experimental sensor study	Adults	–	Breath	ZnO optical fiber sensor	High-sensitivity acetone detection	Potential diagnostic application	No	Technology validation stage
Musa-Veloso et al., 2002	Controlled metabolic study	Healthy adults	8	Breath	GC	Breath acetone reflects ketosis	Nutritional ketosis	No	Non-diabetic cohort
Chou et al., 2024	Review	Mixed age	–	Breath	Various MS platforms	VOC variability and methodological heterogeneity	Biomarker platform challenges	No	Review article
Gudino-Ochoa et al., 2024	Proof-of-concept	Adults	50	Breath	TinyML e-nose	Pattern recognition for diabetes detection	Screening potential	No	No external
Zhou et al., 2025	Technology review	Mixed age	–	Breath	AI photonic sensors	AI-driven VOC pattern recognition	Translational potential	No	Early-stage systems
Woodman et al., 2025	Observational phenotyping	Older adults	300 +	Multi-biomarker (not exclusively VOC)	AI classifiers	Risk stratification in geriatric medicine	Frailty prediction	Yes (not VOC-specific)	Not volatilomics-focused

limitations. Notably, although multiple studies support the association between VOC profiles and metabolic dysregulation in diabetes, only a minority include older subgroups, and none were specifically designed as large-scale longitudinal volatilomic studies in geriatric diabetic cohorts.

3. Advanced technologies in volatilomics: analytical platforms and emerging sensor systems

The advancement of Volatilomics in diabetes and geriatrics relies on high-resolution laboratory platforms and emerging portable sensors [21]. Gas chromatography mass spectrometry (GC–MS) remains the reference standard for qualitative and quantitative VOCs identification, while real-time MS approaches (e.g., Proton-transfer-reaction mass spectrometry (PTR-MS), Selected Ion Flow Tube Mass Spectrometry (SIFT-MS)) and ion-mobility systems support rapid profiling with minimal preparation [27]. Portable e-nose devices based on metal oxide semiconductor (MOS) sensor arrays, coupled with AI classifiers, are accelerating translation toward bedside and home monitoring, despite lower molecular resolution than Mass Spectometetry based methods [28].

4. Artificial intelligence and machine learning in volatilomics

Artificial Intelligence (AI) and Machine Learning (ML) represent key enabling tools in volatilomic research, particularly given the high dimensionality and multivariate nature of VOC datasets [29]. In this context, AI refers to computational systems capable of pattern recognition and predictive modeling, while ML encompasses statistical learning algorithms trained on labeled or unlabeled datasets to identify discriminative VOC signatures [30]. Supervised learning approaches commonly used in VOC analysis include support vector machines (SVM), random forests, artificial neural networks (ANN), and gradient boosting models, which aim to classify disease states or predict metabolic phenotypes [31]. Unsupervised techniques, such as principal component analysis (PCA) and hierarchical clustering, are frequently employed for dimensionality reduction and exploratory stratification [32]. A typical AI-driven volatilomics workflow involves: (i) VOC acquisition via GC–MS or sensor arrays; (ii) preprocessing and normalization; (iii) feature extraction or selection; (iv) model training and cross-validation; and (v) external validation in independent cohorts [33]. However, many published studies remain limited by small training datasets, lack of independent validation cohorts, and potential overfitting [34]. Importantly, while AI-enhanced e-nose platforms have demonstrated promising classification performance in proof-of-concept studies, their clinical applicability in older adults with diabetes remains preliminary [35]. Challenges include interpretability of model outputs, reproducibility across platforms, and regulatory-grade validation. Notably, many machine learning approaches used in volatilomics are distribution-agnostic and therefore less dependent on parametric assumptions; however, appropriate preprocessing and validation strategies remain crucial to ensure robustness.

5. Diabetes in the aging organism: complexity and heterogeneity

The clinical expression of diabetes in older adults is remarkably diverse, reflecting the interplay between biological aging processes, accumulated comorbidities, and social as well as functional determinants of health [36]. Unlike younger patients, where diabetes often follows a more predictable metabolic trajectory, in the geriatric population the disease course is profoundly shaped by heterogeneity [37]. Some individuals remain metabolically stable and functionally independent despite long-standing hyperglycemia, while others experience

rapid deterioration, frailty, and disability [38]. This variability is underpinned by multiple age-related mechanisms that interact with diabetic pathophysiology and influence both traditional and novel biomarkers, including volatilomics signatures [39,40].

5.1. Biological determinants of VOC signatures

Aging-related mitochondrial decline is amplified in diabetes, promoting insulin resistance and β-cell dysfunction and shifting VOC outputs toward oxidative stress–related derivatives such as alkanes and aldehydes, detectable in breath and other biological matrices [41]. In parallel, the gut microbiome undergoes profound age-associated shifts, including reduced diversity and increased prevalence of pathobionts [42]. In diabetes, these alterations are further accentuated, leading to changes in short-chain fatty acid production, impaired gut barrier integrity, and increased systemic endotoxemia [43,44]. Such microbial remodeling directly influences the volatilome, as microbial fermentation contributes to exhaled and secreted VOCs, including ethanol, acetone derivatives, and sulfur-containing compounds[45]. The gut–liver–brain axis, already dysregulated in aging, thus becomes a critical determinant of metabolic VOCs signatures in person with diabetes [46]. Understanding these interactions is essential for disentangling host-derived from microbiome-derived Volatilomics markers [47].

6. Comorbidities, polypharmacy and confounding effects

Older adults with diabetes are rarely affected by the disease in isolation [48] cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, cognitive impairment, and sarcopenia frequently coexist, each contributing to unique metabolic alterations [49]. Moreover, polypharmacy, the use of multiple medications to manage multimorbidity, further complicates the metabolic landscape [50]. Common drugs such as statins, metformin, or ACE inhibitors can modify metabolic pathways and thereby influence the Volatilomics profile [51]. For example, renal insufficiency alters the excretion of nitrogen- and sulfur-containing compounds, while heart failure increases exhaled acetone through enhanced ketone body utilization [52]. These overlapping signals underscore the importance of contextualizing Volatilomics findings within the broader clinical picture of multimorbidity in aging [53].

7. A spectrum of clinical phenotypes

The result of these intertwined processes is a wide spectrum of clinical phenotypes in older adults with diabetes [54]. At one extreme are resilient individuals with preserved function and minimal complications: at the other, frail patients with rapid metabolic decline, recurrent hospitalizations, and severe disability [55]. This heterogeneity underscores the limitations of a “one-size-fits-all” approach and underscores the need for personalized strategies [55]. Volatilomics, by capturing integrated and dynamic metabolic outputs, offers a promising avenue to stratify this heterogeneity and to tailor interventions in line with the principles of precision geriatric medicine [55].

8. A multidimensional approach to VOCs

Historically, diabetes Volatilomics has focused on acetone as a single biomarker, but this reductionist approach cannot capture the heterogeneous and dynamic metabolic landscape of late-life diabetes [56–58]. A multidimensional interpretation of VOCs patterns is therefore required, as oxidative lipid pathways (alkanes/aldehydes), cholesterol biosynthesis (isoprene), and microbial fermentation (ethanol/sulfur volatiles) jointly shape diabetes- and aging-related signatures [59] (Fig. 1). When coupled with AI and ML, Volatilomics technologies can extract clinically meaningful VOCs patterns from complex datasets in

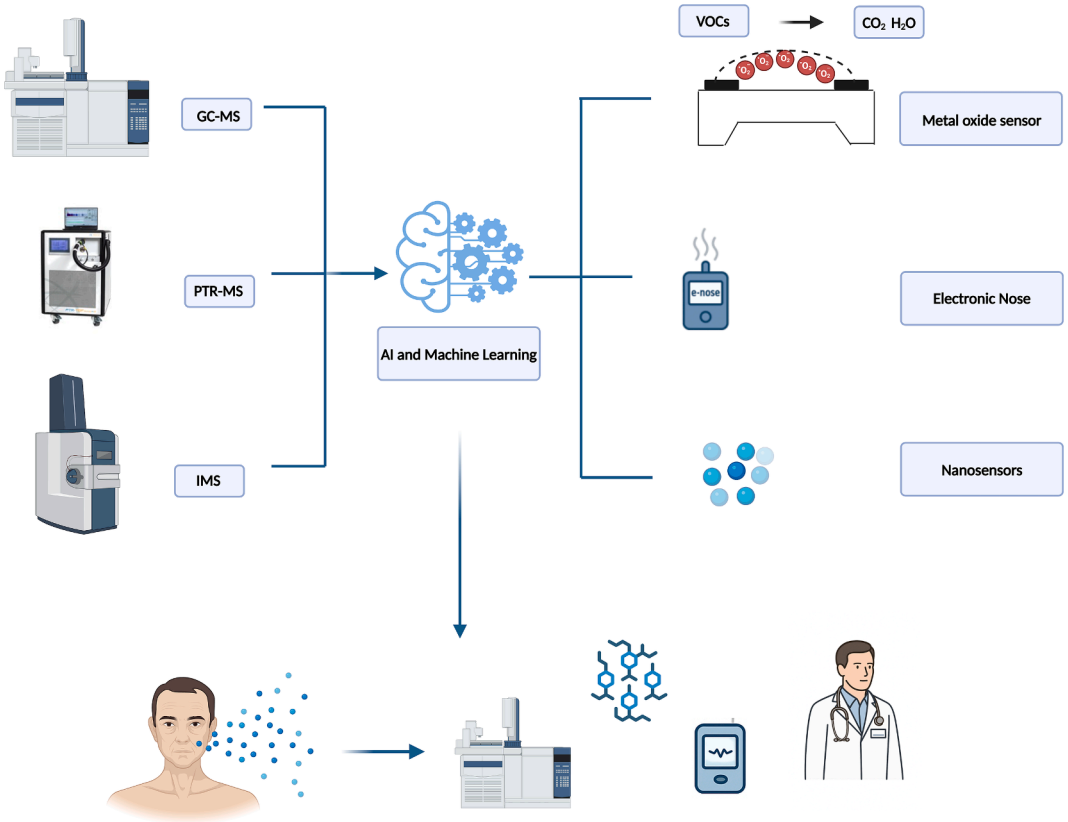

Fig. 1.

late-life. Preliminary AI-based classifiers have demonstrated the potential to distinguish clinical phenotypes in exploratory datasets; however, model interpretability, external validation, and reproducibility across heterogeneous geriatric populations remain open challenges. [60]. This is crucial because multimorbidity and polypharmacy reshape VOCs backgrounds: kidney dysfunction affects nitrogen- and sulfur-containing volatiles, cardiovascular disease modifies lipid-derived VOCs, and drugs such as statins or metformin introduce additional metabolic shifts [61,62]. Viewing VOCs as interconnected network outputs therefore helps disentangle diabetes-specific signals from aging- and treatment-related confounders and enables low-burden, longitudinal monitoring suited to frail older adults [63–65]. Integrated with portable sensors and digital health platforms, this multidimensional approach could translate Volatilomics into practical precision tools for geriatric diabetes care [66–68].

9. Translational and clinical applications

The translational momentum of diabetes Volatilomics is accelerating through sensor miniaturization and AI-assisted analytics [69]. Portable nanosensor platforms and e-noses can identify complex VOCs patterns that go beyond single biomarkers and support real-world monitoring in older adults [70,71]. (Fig. 2). These low-burden tools are particularly suited to geriatric care, where frailty, cognitive decline, and multimorbidity limit invasive testing, and emerging evidence links VOCs panels not only to glycemic excursions but also to oxidative stress, mitochondrial dysfunction, microbiome signals, and complication risk [67,72–74]. In this way, Volatilomics offers the potential to bring precision diagnostics into the everyday management of older adults, shifting care models towards home-based, real-time, and patient-centered monitoring [75].

10. A critical perspective on challenges and open questions

While Volatilomics shows strong promise, several barriers must be addressed before clinical integration in older adults with diabetes. Importantly, the majority of studies available to date are cross-sectional, involve relatively small sample sizes, and were not specifically designed to address geriatric populations with multimorbidity and polypharmacy. Therefore, current findings should be interpreted as hypothesis-generating rather than practice-changing. Key issues include: (i) methodological standardization and cross-platform reproducibility, given VOCs susceptibility to diet, circadian variation, environment, and multimorbidity; (ii) the inadequacy of single-compound strategies (e.g., acetone alone) to represent late-life diabetes complexity; and (iii) the lack of large, multicenter longitudinal geriatric cohorts with harmonized analytical pipelines integrating VOCs with clinical metadata and other omics layers [45,76–78]. Addressing these priorities will be essential for regulatory-grade validation and translation into precision geriatric diabetology.

11. Conclusions

Volatilomics offers a biologically plausible, non-invasive approach to explore metabolic disturbances associated with diabetes and aging. However, most available data derive from mixed-age or proof-of-concept studies, and dedicated validation in older diabetic populations is still lacking. Although proof-of-concept studies support the presence of diabetes-related VOC profiles, clinical translation is limited by variability in sampling and analytical methods, cross-platform inconsistency, and the lack of geriatric-specific validation. Standardized protocols, reproducibility studies, and integration of VOC data with clinical and metabolic markers in large longitudinal cohorts are essential next steps. Such efforts will determine whether volatilomic profiling can advance from experimental observations to a reliable tool for precision diabetes management in aging populations.

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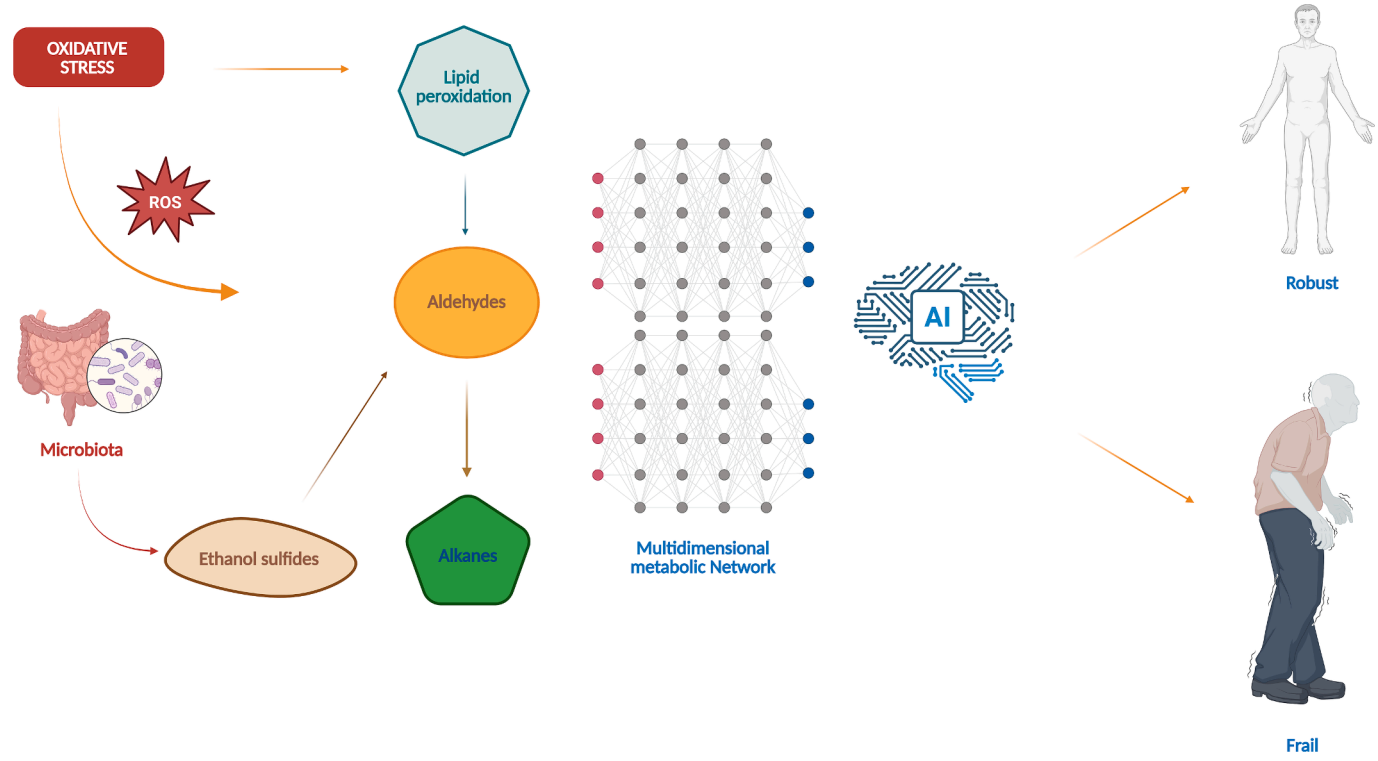

Fig. 2.

Human-cEntred Medicine) Project Code PNC0000003, CUP: B53C22006540001; PRIN2022 – CUP: B53D23020210006, Arketipo: ARtificial Intelligence for Early RisK PrEdicTIon of Heart Failure by Combining Circulating EPi Signature tO Clinical Features Project Code F/310107/01/X56, CUP: B29J23000310005, RENALERT-AI CUP: B29J24000110005,Project Code: F/360062/03/X75.

CRediT authorship contribution statement

Manuela Giovanna Basilicata: Writing – original draft, Visualization, Validation, Conceptualization. **Lucia Scisciola:** Writing – original draft, Data curation, Conceptualization. **Ada Pesapane:** Writing – original draft, Investigation. **Rosaria Anna Fontanella:** Writing – original draft, Investigation. **Nunzia Balzano:** Investigation, Conceptualization. **Alberta Maria Maddalena Palazzo:** Investigation, Conceptualization. **Rashmi Joshi:** Investigation, Conceptualization. **Asad Zia:** Investigation, Conceptualization. **Giovanni Tortorella:** Data curation, Conceptualization. **Zeeshan Ulfat:** Investigation, Conceptualization. **Maryam Arshad:** Investigation, Conceptualization. **Giovanna Aquino:** Validation, Investigation, Conceptualization. **Eduardo Sommella:** Investigation, Data curation, Conceptualization. **Marco Malavolta:** Investigation, Data curation, Conceptualization. **Angelica Giuliani:** Investigation, Data curation, Conceptualization. **Pietro Campiglia:** Supervision, Investigation, Conceptualization. **Michelangela Barbieri:** Investigation, Formal analysis, Conceptualization. **Giuseppe Paolisso:** Writing – original draft, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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