A Systematic Review of the Diagnostic Accuracy of Volatile Organic Compounds in Airways Diseases and their relation to Markers of Type-2 Inflammation

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Supplementary material

1. Search strategy

A PRISMA oriented systematic search was completed from January 1997 to December 2020 using the following sources of evidence, (i) Cochrane library, (ii) Medline and (iii) EMBASE.

Further details on methodology can be found in (PROSPERO - CRD42019141718).

Strategy 577083

| #  | Database | Search term                                      | Results |
|----|----------|--------------------------------------------------|---------|
| 1  | Medline  | ("volatile organic compound*").ti,ab             | 7726    |
| 2  | Medline  | "VOLATILE ORGANIC COMPOUNDS"/                   | 6691    |
| 3  | Medline  | (VOC OR vocs).ti,ab                             | 7212    |
| 4  | Medline  | (exhal*6 OR breath*).ti,ab                       | 113917  |
| 5  | Medline  | EXHALATION/                                      | 3377    |
| 6  | Medline  | (1 OR 2 OR 3)                                   | 14894   |
| 7  | Medline  | (4 OR 5)                                         | 117153  |
| 8  | Medline  | (6 AND 7)                                        | 1107    |
| 9  | Medline  | exp DYSPNEA/                                     | 19644   |
| 10 | Medline  | (breathless* OR dyspn*4).ti,ab                   | 46465   |
| 11 | Medline  | (9 OR 10)                                        | 55084   |
| 12 | Medline  | (8 AND 11)                                       | 5       |
| 13 | Medline  | (asthma*).ti,ab                                  | 146117  |
| 14 | Medline  | exp ASTHMA/                                      | 121260  |
|   | EMBASE                                                                 |   |   |
|---|----------------------------------------------------------------------|---|---|
| 33 | EMBASE ("volatile organic compound*").ti,ab                          |   | 10048 |
| 34 | EMBASE "VOLATILE ORGANIC COMPOUND"/                                   |   | 14083 |
| 35 | EMBASE "VOLATILE ORGANIC COMPOUNDS"/                                 |   | 10777 |
| 36 | EMBASE (voc OR vocs).ti,ab                                           |   | 9092  |
| 37 | EMBASE (33 OR 34 OR 35 OR 36)                                         |   | 20436 |
| 38 | EMBASE (exhal*6 OR breath*).ti,ab                                     |   | 165810 |
| 39 | EMBASE EXHALATION/                                                    |   | 4059  |
| 40 | EMBASE (38 OR 39)                                                     |   | 177809 |
| 41 | EMBASE (37 AND 40)                                                    |   | 1675  |
| 42 | EMBASE (copd).ti,ab                                                   |   | 70312 |
| 43 | EMBASE (((chronic AND obstructive) AND pulmonary) AND disease).ti,ab |   | 59947 |
| 44 | EMBASE "CHRONIC OBSTRUCTIVE LUNG DISEASE"/ OR                        |   | 112227 |
|     | "CHRONIC OBSTRUCTIVE LUNG DISORDER"/ OR                              |   |       |
|     | "CHRONIC OBSTRUCTIVE PSEUDOEMPHYSEMA"/ OR                             |   |       |
|     | "CHRONIC OBSTRUCTIVE PULMONARY DISEASE"/ OR                           |   |       |
|     | "CHRONIC OBSTRUCTIVE PULMONARY DISORDER"/ OR                         |   |       |
|     | "CHRONIC OBSTRUCTIVE RESPIRATORY DISEASE"/                           |   |       |
| 45 | EMBASE (((chronic AND obstructive) AND airway) AND (disease OR coad)).ti,ab |   | 9382 |
| 46 | EMBASE (((chronic AND obstructive) AND lung) AND disease).ti,ab       |   | 24650 |
| 47 | EMBASE ((chronic AND airflow) AND limitation).ti,ab                   |   | 2646  |
EMBASE (((chronic AND obstructive) AND respiratory) AND disease).ti,ab 17649
EMBASE (emphysema).ti,ab 28141
EMBASE exp EMPHYSEMA/ 41697
EMBASE (chronic AND bronchitis).ti,ab 15855
EMBASE "CHRONIC BRONCHITIS"/ 11611
EMBASE exp ASThma/ 237742
EMBASE (asthma*).ti,ab 205990
EMBASE exp PNEUMONIA/ 265756
EMBASE (pneumonia* OR lung inflammation*or respiratory tract infection* OR respiratory infection*).ti,ab 225025
EMBASE exp "HEART FAILURE"/ 443663
EMBASE (heart failure).ti,ab 242128
EMBASE (42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58) 1204355
EMBASE (41 AND 59) 375

Cochrane search:

ID Search
#1 "volatile organic compound*"
#2 MeSH descriptor: [Volatile Organic Compounds] this term only
#3 VOC OR vocs
#4 MeSH descriptor: [Exhalation] this term only
#5 exhal*6 OR breath*
#6 #1 OR #2 OR #3
#7 #4 OR #5

#8 #6 AND #7

#9 asthma*

#10 MeSH descriptor: [Asthma] this term only

#11 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] this term only

#12 copd

#13 (((chronic AND obstructive) AND pulmonary) AND disease)

#14 (((chronic AND obstructive) AND airway) AND (disease OR coad))

#15 (((chronic AND obstructive) AND lung) AND disease)

#16 ((chronic AND airflow) AND limitation)

#17 (((chronic AND obstructive) AND respiratory) AND disease)

#18 (emphysema)

#19 MeSH descriptor: [Emphysema] this term only

#20 (chronic AND bronchitis)

#21 MeSH descriptor: [Bronchitis, Chronic] this term only

#22 {OR #9-#21}

#23 {AND #8-#22}

#24 #8 and #22
### 2. Risk of Bias table (QUADAS2)

Table A: Breakdown of included studies’ risk of bias and applicability concerns

| Asthma studies | Risk of Bias | Applicability concerns |
|----------------|--------------|------------------------|
| Author         | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Olopade et al (1997) | Low | Unclear | Low | Low | Low | Low | Low |
| Paredi et al (2000) | Low | High | Low | Low | Low | Unclear | Low |
| Larstad et al (2007) | Low | High | Low | Low | Unclear | Low | Low |
| Dragonieri et al (2007) | Low | Unclear | Low | Low | Low | Low | Low |
| Fens et al (2009) | Low | Low | Low | Low | Low | Low | Low |
| Ibrahim et al (2011) | High | High | Low | Low | Low | Low | Low |
| Timms et al (2012) | Low | High | High | Low | Low | Low | Low |
| Van der Schee et al (2012) | High | Low | Unclear | Low | Low | Low | Low |
| Schivo et al (2013) | Low | Low | Low | Low | Low | Low | Low |
| Meyer et al (2014) | Low | High | Low | Low | Low | High | Low |
| Schliech et al (2019) | High | Low | Low | Low | Low | Low | Low |
| Brinkman et al (2019) | Unclear | Low | Low | Low | Low | Low | Low |
| Dragonieri et al (2018) | Low | Low | Low | Low | Low | Low | Low |
| Brinkman et al (2019) | Low | High | Low | Low | Low | Low | Low |
| Study                        | 2017 | 2015 | 2010 | 2018 | 2010 | 2010 | 2010 |
|------------------------------|------|------|------|------|------|------|------|
| Plaza et al (2015)           |      |      | High |      |      |      |      |
| Lazar et al (2010)           |      |      |      |      |      |      |      |
| De Vries et al (2018)        |      |      |      |      |      |      |      |
| Montuschi et al (2010)       |      |      |      |      |      |      |      |
| Brinkman et al (2020)        |      |      |      |      |      |      |      |
| COPD studies                 |      |      |      |      |      |      |      |
| Dragonieri et al (2009)      |      |      | High |      |      |      |      |
| Westhoff et al (2010)        |      |      |      | High |      |      |      |
| Basanta et al (2010)         |      |      |      |      |      |      |      |
| Van berkel et al (2010)      |      |      | High |      |      |      |      |
| Fens et al (2011)            |      |      |      |      |      |      |      |
| Cristescu et al (2011)       |      |      |      |      |      |      |      |
| Hattesohl et al (2011)       |      |      | High |      |      |      |      |
| Westhoff et al (2011)        |      |      |      |      |      |      |      |
| Phillips et al (2012)        |      |      |      |      |      |      |      |
| Basanta et al (2012)         |      |      |      |      |      |      |      |
| Study                        | 2013 | 2015 | 2015 | 2015 | 2016 | 2016 | 2017 | 2018 | 2018 | 2019 | 2019 | 2019 |
|------------------------------|------|------|------|------|------|------|------|------|------|------|------|------|
| Martines Sinues et al (2013) | Low  | High | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Shafiek et al (2015)         | Low  | High | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Cazzolla et al (2015)        | Low  | Unclear | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Besa et al (2015)            | Low  | Unclear | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Gaida et al (2016)           | Unclear | Unclear | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Allers et al (2016)          | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Jerno-estaban et al (2017)   | Low  | High | Low  | Low  | Low  | High | Low  | Low  | Low  | Low  | Low  | Low  |
| Pizzini et al (2018)         | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Bregy et al (2018)           | High | High | Unclear | Low  | Unclear | Low  | Unclear | Low  | Unclear | Low  | Unclear | Low  | Unclear |
| Scarlata et al (2018)        | High | High | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Phillips et al (2014)        | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | High |
| Incalzi et al (2012)         | Low  | High | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Rodriguez-Aguilar et al (2019)| Low  | Unclear | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Velzen et al (2019)          | Unclear | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
| Gaugg et al (2019)           | High | High | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  | Low  |
Figure A: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

- Patient Selection
- Index Test
- Reference Standard
- Flow and Timing

Legend:
- High
- Unclear
- Low
Table B: Description of modification of QUADAS-2:

| Risk of Bias         | QUADAS-2                                                                 | Modified QUADAS-2                                                                 |
|----------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| **Patient selection** | Was a consecutive or random sample of patients enrolled?                 | Was patient selection representative of the intended population                   |
|                      | Was a case-control design avoided?                                       | Did the study include disease state and healthy controls                           |
|                      | Did the study avoid inappropriate exclusions?                            | Did the study avoid inappropriate exclusions?                                    |
| **Index test**       | Were the index test results interpreted without knowledge of the results of the reference standard? | Was the index test and data interpretation completed in a standardised and reproducible way? |
|                      | If a threshold was used, was it pre-specified?                           | Was any biomarker validation performed (internal or external)?                    |
| **Reference standard** | Is the reference standard likely to correctly classify the target condition? | Is the reference standards likely to correctly classify the target condition?      |
|                      | Were the reference standard results interpreted without knowledge of the results of the index test? | Removed as not applicable                                                        |
| **Flow and timing**  | Was there an appropriate interval between index test and reference standard? | Was there an appropriate interval between index test and reference standard?      |
|                      | Did all patients receive the same reference standard?                    | Did all patients receive the same reference standard?                            |
|                      | Were all patients included in the analysis?                              | Were all patients included in the analysis?                                      |
| Applicability | QUADAS-2                                                                 | Modified QUADAS-2                                                                 |
|--------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| **Patient selection** | Are there concerns that the included patients and setting do not match the review question? | Are there concerns that the included patients and setting do not match the review question? |
| **Index test** | Are there concerns that the index test, its conduct, or interpretation differs from the review question? | Could the conduct or interpretation of the index test have introduced bias? |
| **Reference standard** | Are there concerns that the target condition as defined by the reference standard does not match the question? | Are there concerns that the target condition as defined by the reference standard does not match the question? |

Index test: Exhaled breath analysis

Reference standard: Internationally accepted standard for diagnosing asthma and COPD (i.e. following GINA and GOLD guidelines)

Target condition: Asthma and COPD

Intended use of the index test: diagnostic
### 3. PRISMA Checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**     |   |                                                                                                                                                                                                                                                                                                                                           |                   |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                     | 1                 |
| **ABSTRACT**  |   |                                                                                                                                                                                                                                                                                                                                           |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.                   | 3                 |
| **INTRODUCTION** |   |                                                                                                                                                                                                                                                                                                                                            |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                                                          | 4-5               |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                           | 5                 |
| **METHODS**   |   |                                                                                                                                                                                                                                                                                                                                           |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                                                      | 3                 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                                                                               | 7-8               |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                                                      | 7-8               |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                                                             | Supplementary material |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                                                                 | 7                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                                                             | 7-8               |
| Section/topic | # | Checklist item | Reported on page # |
|---------------|---|----------------|-------------------|
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7-8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7-8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | N/A |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. | N/A |

### RESULTS

| Section/topic | # | Checklist item | Reported on page # |
|---------------|---|----------------|-------------------|
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 and Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8,9,10,11 and Tables 1-2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 8 and supplementary material |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9-11 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | N/A |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Supplementary material |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
### DISCUSSION

| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |
|---------------------|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Limitations         | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                                                       |
| Conclusions         | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                                                                 |

### FUNDING

| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                 |
|---------|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Funding**

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097*

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org)

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| Compound and chemical classification | Author | Disease | Comments |
|-------------------------------------|--------|---------|----------|
| 1. Carbonyl containing              |        |         |          |
| 1.1. Aldehydes                      |        |         |          |
| 2-oxoglutaric acid semi-aldehyde    | Bregy et al [83] | COPD vs. controls | Analysis by SESI-MS - high levels in COPD patients |
| aspartic acid semi-aldehyde         | Bregy et al [83] | COPD vs. controls | Analysis by SESI-MS - high levels in COPD patients |
| Benzaldehyde                        | Phillips et al [38] | COPD vs. controls | |
| Butanal                             | Rodriguez-Aguilar et al [40] | COPD vs. controls | Positively correlated to COPD |
| Decanal                             | Basanta et al [21] | COPD vs. controls | Identifying COPD (GC-TOF-MS) |
| Dodecanal                           | Basanta et al [21] | COPD vs. controls | Identifying COPD (GC-TOF-MS) |
| Hexanal                             | Basanta et al [21] | COPD vs. controls | Identifying COPD (GC-TOF-MS) |
| Hexanal                             | Jareno-estaban et al [46] | COPD vs. controls | Discriminates between COPD and healthy controls |
| Hexanal                             | Phillips et al [38] | COPD vs. controls | |
| Nonanal                             | Basanta et al [21] | COPD vs. controls | Identifying COPD (GC-TOF-MS) |
| Nonanal                             | Jareno-estaban et al [46] | COPD vs. controls | Discriminates smokers and former smokers (with and without COPD) and never smokers |
| Nonanal                             | Schliech et al [18] | Asthma | Discriminates paucigranulocytic and neutrophilic asthma (Higher in neutrophilic asthma) |
| Nonanal                             | Schliech et al [18] | Asthma | Discriminates eosinophilic and neutrophilic asthma (Higher in neutrophilic asthma) |
| Octanal                             | Brinkman et al [75] | Asthma | Association between exhaled breath VOCs and urinary levels of salbutamol and OCS |
| Compound                  | Authors         | Study Type | Correlation/Method                                      |
|---------------------------|-----------------|------------|--------------------------------------------------------|
| Pentadecanal              | Basanta et al [21] | COPD vs. controls | Identifying COPD (GC-TOF-MS) |
| Pentadecanal              | Ibrahim et al [15] | Asthma vs. controls | Negatively correlated to asthma |
| Undecanal                 | Basanta et al [21] | COPD vs. controls | Identifying COPD (GC-TOF-MS) |
| 3-methyl-propanal         | Rodriguez-Aguilar et al [40] | COPD vs. controls | Positively correlated to COPD |

### 1.2. Esters

| Compound                  | Authors         | Study Type | Correlation/Method                                      |
|---------------------------|-----------------|------------|--------------------------------------------------------|
| Ethyl 2,2-dimethylacetoacetate | Ibrahim et al [15] | Asthma vs. controls | Positively correlated to asthma |
| Linalylacetate            | Gaida et al [47] | COPD vs. controls | VOCs seem to be related to COPD |

### 1.3. Ketones

| Compound                  | Authors         | Study Type | Correlation/Method                                      |
|---------------------------|-----------------|------------|--------------------------------------------------------|
| 2-butanone                | Allers et al [82] | COPD vs. controls | IMS - smoking related compounds |
| 2-butanone                | Ibrahim et al [15] | Asthma vs. controls | Positively correlated to asthma |
| 2-hexanone                | Schliech et al [18] | Asthma | Discriminates pauci-granulocytic and eosinophilic asthma (lower in eosinophilic asthma) |
| 2-pentanone               | Allers et al [82] | COPD vs. controls | Detected by GC-APCI-MS discriminates COPD from healthy volunteers |
| 2-pentanone               | Pizzini et al [32] | Acute and stable COPD vs. controls | Indicative of acute exacerbation of COPD (positive correlation) |
| 4-heptanone               | Pizzini et al [32] | Acute and stable COPD vs. controls | Indicative of acute exacerbation of COPD (positive correlation) |
| 6-methyl-5-hepten-2-one   | Pizzini et al [32] | Acute and stable COPD vs. controls | Non-specific. Significant difference between COPD and healthy volunteers (higher in healthy) |
| Acetone                   | Martines et al [80] | COPD vs. controls | Discriminate COPD from healthy volunteers using IMS |
| Cyclohexanone             | Pizzini et al [32] | Acute and stable COPD vs. controls | Indicative of acute exacerbation of COPD (positive correlation) |
| Chemical Name                | Authors                | Study Type        | Result                                                                                     |
|-----------------------------|------------------------|-------------------|-------------------------------------------------------------------------------------------|
| Cyclohexanone (CAS 108-94-1)| Westhoff *et al* [76]  | COPD vs. controls | IMS identified - raised in COPD patients                                                   |
| Cyclopentanone              | Rodriguez-Aguilar *et al* [40] | COPD vs. controls | Positively correlated to COPD                                                             |

### 1.4. Organic acids

| Chemical Name                | Authors                | Study Type        | Result                                                                                     |
|-----------------------------|------------------------|-------------------|-------------------------------------------------------------------------------------------|
| 11-hydroxyundecanoic acid   | Bregy *et al* [83]     | COPD vs. controls | Analysis by SESI-MS - low levels in COPD patients                                           |
| 2-hydroxyisobutyric acid    | Bregy *et al* [83]     | COPD vs. controls | Analysis by SESI-MS - compound predictive that breath is from a COPD patient               |
| 2-methyl butanoic acid      | Rodriguez-Aguilar *et al* [40] | COPD vs. controls | Negatively correlated to COPD                                                              |
| Acetic acid                 | Phillips *et al* [38]  | COPD vs. controls |                                                                                           |
| Butanoic acid               | Basanta *et al* [21]   | COPD vs. controls | Identifying COPD (GC-TOF-MS) - negative correlation                                         |
| Dodecanedioic acid          | Bregy *et al* [83]     | COPD vs. controls | Analysis by SESI-MS - low levels in COPD patients                                           |
| Oxoheptadecanoic acid       | Bregy *et al* [83]     | COPD vs. controls | Analysis by SESI-MS - low levels in COPD patients                                           |
| Pentanoic acid              | Basanta *et al* [21]   | COPD vs. controls | Identifying COPD (GC-TOF-MS) - negative correlation                                         |
| Lysine                      | Brinkman *et al* [75]  | Asthma            | Association between exhaled breath VOCs and urinary levels of salbutamol and OCS          |
| Glycolic acid               | Brinkman *et al* [75]  | Asthma            | Association between exhaled breath VOCs and urinary levels of salbutamol and OCS          |
| ω-oxo-alkenoic acids        | Gaugg *et al* [33]     | COPD              | Levels significantly reduced in frequent COPD exacerbators                                 |
| ω-hydroxy acids             | Gaugg *et al* [33]     | COPD              | Levels significantly reduced in frequent COPD exacerbators                                 |

### 2. Hydrocarbons

#### 2.1. Alkanes
| Compound                        | Author et al. [Ref] | Study Type          | Findings                                                                 |
|--------------------------------|---------------------|---------------------|--------------------------------------------------------------------------|
| 3,7-dimethylnonane             | Schliech et al [18] | Asthma              | Discriminates eosinophilic and neutrophilic asthma (Higher in neutrophilic asthma) and lower eosinophilic asthma |
| Hexane                         | Schliech et al [18] | Asthma              | Discriminates paucigranulocytic and eosinophilic asthma (lower in eosinophilic asthma) |
| Undecane                       | Schliech et al [18] | Asthma              | Discriminates paucigranulocytic and neutrophilic asthma (Higher in paucigranulocytic asthma) |
| 2,6-Dimethyl-heptane           | Van Berkel et al [19]| COPD vs. controls  | Classification model differentiated COPD from healthy volunteers         |
| 4,7-Dimethyl-undecane          | Van Berkel et al [19]| COPD vs. controls  | Classification model differentiated COPD from healthy volunteers         |
| 4-Methyl-octane                | Van Berkel et al [19]| COPD vs. controls  | Classification model differentiated COPD from healthy volunteers         |
| Hexadecane                     | Van Berkel et al [19]| COPD vs. controls  | Classification model differentiated COPD from healthy volunteers         |
| 6-ethyl-2-methyl-Decane        | Cazzola et al [39]  | COPD vs. controls  | Positively correlated to COPD                                           |
| Decane                         | Cazzola et al [39]  | COPD vs. controls  | Positively correlated to COPD                                           |
| Hexane, 3-ethyl-4-methyl-       | Cazzola et al [39]  | COPD vs. controls  | Negatively correlated to COPD                                           |
| Tridecane                      | Gaida et al [47]    | COPD vs. controls  | VOCs seem to be related to COPD                                         |
| Tetradecane                    | Rodriguez-Aguilar et al [40]| COPD vs. controls  | Negatively correlated to COPD                                           |
| 2-methyl-decane                | Ibrahim et al [15]  | Asthma vs. controls| Positively correlated to asthma                                         |
| 2,6,10-trimethyl-dodecane      | Ibrahim et al [15]  | Asthma vs. controls| Positively correlated to asthma                                         |
| 2,6,11-trimethyl-dodecane      | Ibrahim et al [15]  | Asthma vs. controls| Positively correlated to asthma                                         |
| 5,5-Dibutylnonane              | Ibrahim et al [15]  | Asthma vs. controls| Negatively correlated to asthma                                         |
| Pentane                        | Olopade et al [29]  | Acute and stable asthma vs. controls | Raised in asthma |
| Compound                        | Authors         | Conditions                        | Observations                                           |
|--------------------------------|-----------------|-----------------------------------|-------------------------------------------------------|
| Ethane                         | Paredi et al [36] | Asthma vs. controls               | Raised in asthma                                       |
| Butane                         | Phillips et al [38] | COPD vs. controls                 | Undetermined correlation                               |
| 2,4-dimethylheptane            | Pizzini et al [32] | Acute and stable COPD vs. controls | Lower in COPD exacerbations compared to healthy volunteers |
| 2,6-dimethyloctane             | Pizzini et al [32] | Acute and stable COPD vs. controls | Lower in COPD exacerbations compared to healthy volunteers |
| 2-methylhexane                 | Pizzini et al [32] | Acute and stable COPD vs. controls | Higher in COPD exacerbations compared to healthy volunteers |
| cyclohexane                    | Pizzini et al [32] | Acute and stable COPD vs. controls | Higher in COPD exacerbations compared to healthy volunteers |
| n-butane                       | Pizzini et al [32] | Acute and stable COPD vs. controls | Indicative of acute exacerbation of COPD (negative correlation) |
| n-Heptane                      | Pizzini et al [32] | Acute and stable COPD vs. controls | Indicative of stable COPD (positive correlation)       |

### 2.2. Alkenes

| Compound                        | Authors         | Conditions                        | Observations                                           |
|--------------------------------|-----------------|-----------------------------------|-------------------------------------------------------|
| 3- tetradecene                 | Schliech et al [18] | Asthma               | Discriminates paucigranulocytic and neutrophilic asthma (Higher in neutrophilic asthma) |
| Pentadecene                    | Schliech et al [18] | Asthma               | Discriminates paucigranulocytic and neutrophilic asthma (Higher in neutrophilic asthma) |
| Isoprene                       | Van Berkel et al [19] | COPD vs. controls | Classification model differentiated COPD from healthy volunteers |
| 1-Pentene, 2,4,4-trimethyl-     | Cazzola et al [39] | COPD vs. controls               | Negatively correlated to COPD                          |
| 1,6-Dimethyl-1,3,5-heptatriene | Gaida et al [47] | COPD vs. controls               | VOCs seem to be related to COPD                       |
| 3,5-heptatriene                | Gaida et al [47] | COPD vs. controls               | VOCs seem to be related to COPD                       |
| Isoprene                       | Phillips et al [38] | COPD vs. controls               | Differentiating stable COPD patients                   |
### 2.3. Hydrocarbons

| Compound                  | Authors               | Study Group         | Correlation                           |
|---------------------------|-----------------------|---------------------|---------------------------------------|
| C16 hydrocarbon           | Van Berkel *et al* [19]| COPD vs. controls   | Classification model differentiated COPD from healthy volunteers |
| 4-ethyl-o-xylene          | Ibrahim *et al* [15]  | Asthma vs. controls | Negatively correlated to asthma        |
| Isoprene                  | Lastard *et al* [67]  | Asthma vs. controls | Low in asthmatics                      |
| Nonadecane                | Phillips *et al* [38] | COPD vs. controls   | Undetermined correlation               |
| Octane                    | Rodriguez-Aguilar *et al* [40] | COPD vs. controls | Positively correlated to COPD          |

### 2.4. Monoaromatics

| Compound                  | Authors               | Study Group         | Correlation                           |
|---------------------------|-----------------------|---------------------|---------------------------------------|
| Benzene, 1,3,5-tri-tert-butyl- | Cazzola *et al* [39]  | COPD vs. controls   | Negatively correlated to COPD          |
| 1-Ethyl-3-methyl benzene  | Gaida *et al* [47]    | COPD vs. controls   | VOCs seem to be related to COPD        |
| m/p-Xylene                | Gaida *et al* [47]    | COPD vs. controls   | VOCs seem to be related to COPD        |
| O-xylene                  | Gaida *et al* [47]    | COPD vs. controls   | VOCs seem to be related to COPD        |
| Benzene                   | Phillips *et al* [38] | COPD vs. controls   | Undetermined correlation               |
| Toluene                   | Phillips *et al* [38] | COPD vs. controls   | Undetermined correlation               |

### 2.5. Terpenes

| Compound                  | Authors               | Study Group         | Correlation                           |
|---------------------------|-----------------------|---------------------|---------------------------------------|
| Limonene                  | Cazzola *et al* [39]  | COPD vs. controls   | Negatively correlated to COPD          |
| Terpinolene               | Ibrahim *et al* [15]  | Asthma vs. controls | Positively correlated to asthma        |
| 4-Carene                  | Brinkman *et al* [75] | Asthma              | Association between exhaled breath VOCs and urinary levels of salbutamol and OCS |

### 3. Alcohol and Phenols
### 3.1. Alcohols

| Compound                              | Authors          | Study Type                  | Correlation                                                                 |
|---------------------------------------|------------------|-----------------------------|----------------------------------------------------------------------------|
| Cyclohexanol                          | Basanta et al [21] | COPD vs. controls           | Identifying COPD (GC-TOF-MS)                                               |
| Bicyclo[2.2.2]octan-1-ol, 4-methyl -  | Brinkman et al [25] | Acute and stable asthma vs. controls | Correlated with sputum eosinophils during loss of asthma control and with FENO during loss of asthma control |
| C9H16O                                |                  |                             |                                                                            |
| Methanol CH3OH                         | Brinkman et al [25] | Acute and stable asthma vs. controls | Correlated with FEV1% predicted during loss of asthma control               |
| 2-Propanol                            | Cazzola et al [39] | COPD vs. controls           | Negatively correlated to COPD                                               |
| 2-Propanol                            | Rodriguez-Aguilar et al [40] | COPD vs. controls | Positively correlated to COPD                                               |
| Phenole                               | Gaida et al [47]  | COPD vs. controls           | VOCs seem to be related to COPD                                             |
| 2-butylcyclohexanol                   | Ibrahim et al [15] | Asthma vs. controls         | Negatively correlated to asthma                                             |
| 2-butyloctanol                        | Rodriguez-Aguilar et al [40] | COPD vs. controls | Positively correlated to COPD                                               |
| Benzyl alcohol                        | Ibrahim et al [15] | Asthma vs. controls         | Positively correlated to asthma                                             |
| Phenol                                | Phillips et al [38] | COPD vs. controls           | Undetermined correlation                                                    |
| 1-propanol                            | Schliech et al [18] | Asthma                      | Discriminates eosinophilic and neutrophilic asthma (Higher in neutrophilic asthma) and lower in eosinophilic asthma |

### 3.2. Phenol derivatives

| Compound                              | Authors          | Study Type                  | Correlation                                                                 |
|---------------------------------------|------------------|-----------------------------|----------------------------------------------------------------------------|
| Butylated hydroxytoluene             | Cazzola et al [39] | COPD vs. controls           | Negatively correlated to COPD                                               |
| m/p-Cresol                            | Gaida et al [47]  | COPD vs. controls           | VOCs seem to be related to COPD                                             |

### 4. Others
### 4.1. Sulphides

| Compound                  | Author(s)          | Group               | Correlation                                                                 |
|---------------------------|--------------------|---------------------|----------------------------------------------------------------------------|
| Phthalic anhydride        | Phillips et al [38] | COPD vs. controls   | Undetermined correlation                                                   |
| Sulphur dioxide           | Phillips et al [38] | COPD vs. controls   | Undetermined correlation                                                   |
| Dimethyl disulfide        | Pizzini et al [32]  | Acute and stable COPD vs. controls | Non-specific. Significant difference between COPD and healthy volunteers (higher in healthy) |
| Methyl propyl sulfide     | Pizzini et al [32]  | Acute and stable COPD vs. controls | Indicative of stable COPD (positive correlation) |

### 4.2. Permanent gases

| Compound                  | Author(s)          | Group               | Correlation                                                                 |
|---------------------------|--------------------|---------------------|----------------------------------------------------------------------------|
| Ethyl 4-nitrobenzoate     | Ibrahim et al [15]  | Asthma vs. controls | Negatively correlated to asthma                                             |
| Indole                    | Martines et al [80]| COPD vs. controls   | Discriminate COPD from healthy volunteers using IMS                        |
| Indole                    | Gaida et al [47]    | COPD vs. controls   | VOCs seems to be related to COPD                                            |

### 4.3. Heterocycles

| Compound                  | Author(s)          | Group               | Correlation                                                                 |
|---------------------------|--------------------|---------------------|----------------------------------------------------------------------------|
| Oxirane-dodecyl           | Basanta et al [21]  | COPD vs. controls   | VOCs seem to be related to COPD                                             |
| γ-hydroxy-L-homoarginine  | Bregy et al [83]    | COPD vs. controls   | Analysis by SESI-MS - compound predictive that breath is from a COPD patient |

### 4.4. Nitriles

| Compound                  | Author(s)          | Group               | Correlation                                                                 |
|---------------------------|--------------------|---------------------|----------------------------------------------------------------------------|
| Ace-tonitrile - C2H3N      | Brinkman et al [25]| Acute and stable asthma vs. controls | Correlated with sputum eosinophils and FEV1% during loss of asthma control |
| Hexyl ethylphosphonofluoridate | Cazzola et al [39]| COPD vs. controls   | Negatively correlated to COPD                                              |

### 4.5. Anhydrides

| Compound                  | Author(s)          | Group               | Correlation                                                                 |
|---------------------------|--------------------|---------------------|----------------------------------------------------------------------------|
| Acetonitrile              | Allers et al [82]   | COPD vs. controls   | IMS - smoking related compound                                              |

### 4.6. Furans
| Compound                        | Authors          | Study Groups          | Correlation                        |
|--------------------------------|------------------|-----------------------|------------------------------------|
| 2-pentylfuran                   | Basanta et al [21]| COPD vs. controls     | Identifying COPD (GC-TOF-MS)       |
| **4.7. Quinones**               |                  |                       |                                    |
| Carbon dioxide                 | Phillips et al [38]| COPD vs. controls     | Undetermined correlation           |
| **4.8. Others**                 |                  |                       |                                    |
| 2,6-Di-tert-butylquinone       | Ibrahim et al [15]| Asthma vs. controls   | Negatively correlated to asthma    |
| 3,4-Dihydroxybenzonitrile      | Ibrahim et al [15]| Asthma vs. controls   | Positively correlated to asthma    |
| Allyl methyl sulphide           | Ibrahim et al [15]| Asthma vs. controls   | Positively correlated to asthma    |

**Table C**: Table outlining reported VOC biomarkers in Asthma and COPD.