biocrates
The future of research and health

Pan-cohort metabolomics – The future of population health

Abstract book

biocrates.com

Virtual event 02nd February 2021

Introduction

As populations age, the challenge is to make sure people are not only living for longer but staying healthy for longer. Epidemiological research contributes greatly to our understanding of what constitutes healthy aging. Population-based cohort studies hold the key to identifying risk factors for common diseases. Today, epidemiologists have a wealth of innovative technologies at their disposal, allowing them to study heritable factors and environmental stimuli as well as microbiome, nutrition and lifestyle.

Metabolomics is one such technology. With metabolomics, we can discover which diseases someone is at risk for – and what can be done to limit the long-term consequences or prevent the disease altogether.

Collaboration beyond local and regional cohorts is crucial in deepening our collective understanding of the gene-lifestyle-environment interaction. The recent push towards collaborative research has also inspired growing interest in making metabolomics data accessible in standardized formats.

At biocrates, we are continually impressed by the great science achieved and shared by metabolomics researchers. Our goal for this symposium was to create a platform for world-leading experts in epidemiology and metabolomics to share their experiences in cohort studies especially in regard to:

– integrating data from different technologies in multi-omics studies
– correlating metabolomics data with exposome and lifestyle factors
– validating their findings in independent cohorts, and
– laying the foundation for making metabolomics data accessible and truly interoperable

The discoveries and methodological groundwork laid by this group will not only benefit researchers who want to use metabolomics in their epidemiological and clinical cohorts, but also pave the way for translation into precision medicine in prevention, clinical care and pharmacological therapy. Ultimately, by sharing our findings, we are all a step closer to improving population health through biomedical research.

We hope this symposium has inspired ideas for your own research and new opportunities to collaborate. We look forward to continuing to work together using metabolomics and multi-omics analyses to advance our knowledge of the biochemistry of health and disease.

From the organizing team,

Dr. Therese Koal
Chief Technology Officer

Dr. Matthias Scheffler
Chief Business Officer

Agenda

Metabolomics – From genetical to environmental influences

Prof. Dr. Annette Peters
Director of the EPI Institute of Epidemiology | Helmholtz Zentrum Munich, Germany

Advancing precision medicine and precision population health in Asia

Prof. Dr. John Chambers
Director, Centre for Global Health Research | Nanyang Technological University, Singapore

Targeted metabolomics across different prospective cohorts in Germany

Dr. Anna Floegel
Department of Epidemiological Methods and Etiological Research | Leibniz Institute for Prevention Research and Epidemiology, Bremen, Germany

The exposome and cancer risk in the EPIC cohort – Results from recent metabolomics studies

Dr. Augustin Scalbert
Group Head Biomarkers Group | International Agency for Research on Cancer, Lyon, France

Metabolomics in the Tohoku Medical Megabank Cohort Project

Prof. Dr. Seizo Koshiba
Advanced Research Center for Innovations in Next-Generation Medicine (INGEM)
Tohoku Medical Megabank Organization | Tohoku University, Sendai, Japan

Cross-platform genetic discovery of small molecule products of metabolism and application to clinical outcomes

Prof. Dr. Claudia Langenberg
MRC Epidemiology Unit, University of Cambridge, UK | Computational Medicine, BIH

Genetics meets metabolomics and beyond: Perspectives for large cohort studies

Prof. Dr. Karsten Suhre
Director of Bioinformatics Core | Weill Cornell Medicine, Doha, Qatar

Lessons learned from metabolomics analyses in human cohorts

Prof. (emer.) Dr. Jerzy Adamski
Head of the GAC, Head of Molecular Endocrinology | Helmholtz Zentrum Munich, Germany

Metabolomics – From genetical to environmental influences

Prof. Dr. Annette Peters

Director of the EPI Institute of Epidemiology
Helmholtz Zentrum Munich, Germany

Abstract

Population-based cohort studies allow to evaluate the role of risk factors in disease development. Metabolites measured in blood and urine offer immense insights into understanding of disease occurrence and progression. Groundbreaking evidence was generated when genome-wide association studies used targeted and untargeted metabolomics serum profiles. For the first time, single nucleotide polymorphisms were able to explain a substantial amount of variability in certain metabolites.

Systematic evaluation followed linking metabolite profiles to age and sex discovering and describing substantial metabolic differences over the life-course. Metabolite profiles showed to be highly predictive of major chronic diseases such as myocardial infarction and type 2 diabetes. Similarly, medications such as metformin were shown to influence metabolite profiles which in part are able to explain other positive side effects of this treatment.

Current developments improving the resolutions of the metabolite measurements and the annotations of the measured profiles allow to capture low abundant xenobiotics, food derivatives and degradation products in human biosamples. Thereby, future studies will be able to characterize endogenous doses of exogenous chemicals as well as the early pathophysiological responses towards environmental exposures.

Large mega cohorts such as the German National Cohort NAKO provide high quality biosamples, that will serve to understand the complexity of human disease development for future generations. It is considered very likely that blood and urine based metabolomic profiles will play an important and integral role in paving novel paths to diagnosis, treatment and prevention of human diseases.

Watch recording

Questions and answers

? You mentioned the microbiome; where do you see the biggest impact of the microbiome to human health when you‘re looking at your epidemiological cohort studies?

Understanding the link between metabolites and microbiome will be exciting because evolutionary, humans have diverted the generation of many metabolites needed, to the microbiota, which live in and on our body. It‘s more and more apparent that healthy environments rich in different microbiota, such as, for example, farm environments can diminish the risk for allergic diseases. However, for other diseases, such as cardiovascular disease, neurodegenerative diseases or diabetes, the associations will also be discovered. Some metabolites connected with type two diabetes, for example, are actually likely not to be generated by the host, but by the microbiota in our body.

? A question regarding healthy aging: What is your opinion? What are the main factors? From metabolomics to metabolic pathways, which we can influence regarding reducing our own risk factors to really follow the passion, to have a better healthy aging.

Aging is, from a molecular perspective, a very complex endeavor. My answer as an epidemiologist is very standard: Eat healthy, do not smoke, exercise regularly and do not drink too much. And then, as an environmental epidemiologist, of course, we are aware that drivers, such as air pollution, are linked to health at all ages. There are also other environmental chemicals, which we know through in-depth metabolomics and identified as having an influence on disease and healthy aging. That said, there is the idea that you can also drive internal pathways pharmacologically, such as preventing protein misfolding, reducing telomere shortening, reducing mutations and so forth. However, as an epidemiologist I would rather point to the lifestyle modifications.

Advancing precision medicine and precision population health in Asia

Prof. Dr. John Chambers

Director, Centre for Global Health Research
Nanyang Technological University, Singapore

Watch recording

Questions and answers

? You highlighted in the beginning of your talk that “What we have measured so far [genome, lifestyle] doesn’t explain the higher incidence of diabetes in Asian populations”. Can you speculate what parameter could be most promising?

20 years ago I placed a bet. It was wrong. I’m not going to make a second wrong bet. I think that it’s not genetic. I think we also know that these complex diseases are often set up earlier in life. Looking cross-sectionally and at metabolite profiles now is not going to be necessarily so informative, but I think if we turn the clock back and start to look at the behaviors and the genomic regulation or metabolic disease regulation that comes with it. I’m quite a big fan of epigenetics. I think that’s been more informative.

? Have you been looking into the impact of the microbiome? [Concerning the different incident rates between European and Asian populations regarding diabetes]. Especially the influence of mother milk and the microbiota is highly discussed these days.

We haven’t looked at it, yet. We’ve been planning to do it, so we’ve collected the relevant biosamples but we don’t have any data that we can talk about. Now we can plan out what experiments to be next. So that in three year’s time, Jerzy Adamski can come back and chair a session where we solve the problem.

Targeted metabolomics across different prospective cohorts in Germany

Dr. Anna Floegel

Department of Epidemiological Methods and Etiological Research
Leibniz Institute for Prevention Research and Epidemiology,
Bremen, Germany

Abstract

Targeted metabolomics data is available in multiple prospective cohorts in Germany and offers a great chance for pan-cohort metabolomics. In two German cohorts (EPIC-Potsdam and EPIC-Heidelberg), we studied associations between serum metabolites including acylcarnitines, amino acids, hexose and phospholipids, and risk of cardiovascular diseases.

For this purpose, we used samples from two case-cohort studies in EPIC-Potsdam and EPIC-Heidelberg with random subcohorts of n=2214 and n=770 each, and including n=204 and n=228 incident cases of myocardial infarction as well as n=147 and n=121 incident cases of stroke, respectively. Using a meta-analytical approach, we found that higher concentrations of several sphingomyelins, acyl-alkyl- and diacyl-phosphatidylcholines were linked to a higher risk of myocardial infarction in both cohorts. No consistent associations were observed between serum metabolites and stroke risk. Furthermore, in subsamples of four German cohorts namely KORA (n=3029), EPIC-Potsdam (n=2458), CARLA (n=1427) and EPIC-Heidelberg (n=812), we aimed to better understand metabolic differences between diverse cohorts.

Therefore, we used measurements of 100 serum metabolites that have been collected in all four studies with different kits and constructed metabolite networks with Gaussian Graphical Modelling for each cohort. We then compared the metabolite networks across cohorts and found moderate to high similarity. The highest similarity of metabolite networks was observed for EPIC-Potsdam with CARLA and KORA. Eventually we constructed a meta-analytic network combining targeted metabolomics data of the four original studies. Pan-cohort metabolomics has been applied to different German prospective cohorts; it should move to European and global level as it provides rich datasets which can be the basis for complex analyses addressing population health.

Watch recording

Questions and answers

?

How can we decipher which metabolites are from the microbiome/human body. Is it duable in children at early age?

So in our ongoing metabolomic study in the children cohorts, we only include children from 3-15 years, although we have biosamples from age 3 months up. But you are right, for metabolites from the microbiome this would probably be too early. With 3 years though, the children eat normal food. As our children cohort study is concerned about the food metabolome we also expect to find metabolites derived from the microbiome.

?

Did you select specific metabolites as reference for good quality within a cohort and how many would you recommend for cohort combining and correction process?

We included quality control samples (so the same sample multiple times on multiple plates during metabolomic analysis). We then excluded metabolites with high coefficient of variation in these quality controls before the analysis. That is why we had only 100 metabolites in the final analysis, the kits include more metabolites, but there are always many of them below detection limit etc... You could check out this publication for further details: Floegel et al. Reliability of serum metabolite concentrations over a 4-month period using a targeted metabolomics approach. PLoS One. 2011;6(6):e21103.

The exposome and cancer risk in the EPIC cohort – Results from recent metabolomics studies

Dr. Augustin Scalbert

Group Head | Biomarkers Group
International Agency for Research on Cancer, Lyon, France

Abstract

Major risk factors for cancer have been identified but the causes of several types of cancer remain largely unknown. Metabolomic approaches can be used to measure hundreds to thousands of metabolites in blood or urine and to explore the role of environmental exposures in cancer etiology.

Exogenous metabolites derived from diet, drugs, contaminants or microbiota, provide direct information on exposures. Endogenous metabolites whose levels can be influenced by environmental exposures, provide information on biochemical mechanisms linking exposures to cancer. Both were measured using both targeted and untargeted metabolomics approaches in various studies nested in the European Prospective Investigation on Cancer and nutrition (EPIC) cohort. Applied to case-control studies, these studies revealed new associations between metabolites such as amino acids, lipids, and xenobiotics with cancer outcomes, several years before diagnosis.

The same metabolomics approaches applied to cross-sectional studies led to the discovery of novel biomarkers of exposure for cancer risk factors and body habitus useful to assess exposures not easily measured with questionnaires. Recent results obtained in the EPIC cohort will be presented and specific areas where methodological progress in metabolomics is more particularly needed will be discussed.

http://exposome-explorer.iarc.fr/

Watch recording

Questions and answers

?

How can we improve the FFQ [Food frequency questionnaire] because they seem too broad compared to the complexity of the metabolome and the exposome?

FFQ have their limitations indeed, in particular for the number of food items that can be included in the questionnaire. Measuring the internal exposome and biomarkers of intake allows to collect information on food items that have not been documented in the questionnaires. In some cohort studies, we have limited information on specific exposures. For example, some cohorts may have detailed information on some environmental factors and no information on the diet, or alcohol intake. Measuring the internal exposome may provide this information, even when collection was not planned in advance.

?

Do you suggest any specific time of the day for sampling, to study exposome based metabolomics?

There is no single answer to this: I don't think we could say that there is perfect time of sampling. As mentioned before, timing is very important when you have just one sample in large cohorts studies collected at baseline to know how reproducible these measurements are. So this is some data we've collected also in the exposomics program.
When you think about these dietary compounds, some may be relatively variable when they are measured after the meal, and then stabilize during fasting conditions.
We've worked with both types of samples before, and some metabolites and dietary compounds we measured we think could be less variable if you're using fasting samples.

Metabolomics in the Tohoku Medical Megabank Cohort Project

Prof. Dr. Seizo Koshiba

Advanced Research Center for Innovations in Next-Generation Medicine (INGEM), Tohoku Medical Megabank Organization
Tohoku University, Sendai, Japan

Abstract

Tohoku Medical Megabank (TMM) Project conducts two prospective cohort studies for more than 150,000 individuals in Japan. One is the TMM Community-Based Cohort Study targeting adult residents, and the other is the TMM Birth and Three-Generation Cohort Study targeting pregnant women with their infants, husbands, and both grandparents.

After the baseline surveys (2013-2017), we are conducting first repeat surveys (2017-2021) and will start second repeat surveys from 2021. During the surveys, we have collected many kinds of information (questionnaires [life styles, medical history, etc.], blood and physiological tests, MRI, etc.) and samples (plasma, serum, urine, etc.). Based on the collected samples, we have conducted multi-omics analyses (genome, metabolome, etc.) and have already obtained whole genome sequence data from more than 8,000 participants and the plasma metabolome data from more than 25,000 participants. The statistical information of each omics layer are available from our database, Japanese Multi Omics Reference Panel (jMorp; https://jmorp.megabank.tohoku.ac.jp/).

In this database, we provide many kinds of metabolome information, such as distribution of metabolites, correlation between metabolites, and the change of metabolome of individuals between baseline and repeat surveys. These results have been used as a reference information for many kinds of research. We are also investigating associations of metabolome with genome or the collected cohort data. Especially, based on the metabolome genome-wide association study (MGWAS), we identified many kinds of metabolites affected by genetic polymorphisms. We will discuss the importance of metabolome analysis for large scale prospective cohort studies.

jMorp; https://jmorp.megabank.tohoku.ac.jp/

Watch recording

Questions and answers

? Why did you start shifting to targeted platforms for your population studies [from non-targeted metabolomics]?

At first, we started non-target type analysis based on mass spectrometry, but during our research we found the stability not to be as good compared with target type analysis. So we changed to target analysis. First with a gas chromatography based setup. During the last two years, we changed to chromatography based [analysis] using biocrates kits. We found that the stability is better compared to other methods.

? Concerning your jMorp database and your meta data, which are in there. Can everybody access the underlying data?

At present, we are providing statistical data on jMorp to Japanese people and individuals data can be accessed, but only based on the permission of a committee. We only provide statistical data to foreign countries and conducted several cooperation studies with cohort groups from 14 countries. [This included] especially meta GWAS. If you want information, please contact me. Especially for statistical data or GWAS.

Cross-platform genetic discovery of small molcule products of metabolism and application to clinical outcomes

Prof. Dr. Claudia Langenberg

MRC Epidemiology Unit, University of Cambridge, UK
Computational Medicine, BIH

Abstract

Circulating levels of small molecules or metabolites are highly heritable, but the impact of genetic differences in metabolism on human health is not well understood. In this cross-platform, genome-wide meta-analysis of 174 metabolite levels across six cohorts including up to 86,507 participants (70% unpublished data), we identify 499 (362 novel) genome-wide significant associations ($p<4.9\times10-10$) at 144 (94 novel) genomic regions.

We show that inheritance of blood metabolite levels in the general population is characterized by pleiotropy, allelic heterogeneity, rare and common variants with large effects, non-linear associations, and enrichment for nonsynonymous variation in transporter and enzyme encoding genes. The majority of identified genes are known to be involved in biochemical processes regulating metabolite levels and to cause monogenic inborn errors of metabolism linked to specific metabolites, such as ASNS (rs17345286, MAF=0.27) and asparagine levels.

We illustrate the influence of metabolite-associated variants on human health including a functional variant (rs17681684) in GLP2R associated with citrulline levels, impaired insulin secretion and type 2 diabetes risk. We link genetically-higher serine levels to a 95% reduction in the likelihood of developing macular telangiectasia type 2 (odds ratio (95% confidence interval) per standard deviation higher levels 0.05 (0.03-0.08; $p=9.5\times10-30$)). We further demonstrate the predictive value of genetic variants identified for serine or glycine levels for this rare and difficult to diagnose degenerative retinal disease (area under the receiver operating characteristic curve: 0.73 (95% confidence interval: 0.70-0.75)), for which low serine availability, through generation of deoxysphingolipids, has recently been shown to be causally relevant.

These results show that integration of human genomic variation with circulating small molecule data obtained across different measurement platforms enables efficient discovery of genetic regulators of human metabolism and translation into clinical insights.

https://www.omicscience.org/

Watch recording

Questions and answers

?

Can you explain a little bit more what citrulline is doing in diabetes. Is it a liver gut excess mechanism?

I don't have a confident answer what citrulline itself is doing, we see citrulline as a marker of GLP2R signaling.
Chronic difference in signaling leads to differences in incretins (and difference in K-cells) that secrete these incretins. If this is a chronic process and is constantly elevated leads to a desensitization of the relevant receptors on cells in the pancreas. This in turn explains the reduced insulin secretion and increased risk of type two diabetes of these patients. We don't think this is necessarily a citrulline effect per se, but citrulline is a marker of the activity that's going on with the driver driving that association with type two diabetes.

?

What is your opinion about the value of metabolomics to contribute into new insights and better understanding of these metabolic commonalities between diseases like low grade inflammation, immunity, or insulin resistance? Or can we treat insulin resistance to avoid manifestation of type two diabetes?

That's a wonderful question. We've just completed a study where we´ve looked at metabolites and their associations with a whole range of different (over 26) incident diseases. The purpose was to distinguish those associations that are specific to a given disease versus non-specific or ubiquitously shared. We integrated all the information we already had on existing risk factors, things that we know about in clinical practice sometimes already managed and how that may drive some of the observed associations.
That brings us back, that you can identify risk factors. I think that's the power. And we were privileged to be able to do this in a large scale historical cohort where all of this information was in one place. I think those are some of the opportunities that highlight what can be done. The message that I would like to take from that work is also that it is important to not look at metabolites or at diseases in isolation. Because [otherwise] a large part of the story is ignored.

Genetics meets metabolomics and beyond: Perspectives for large cohort studies

Prof. Dr. Karsten Suhre

Director of Bioinformatics Core
Weill Cornell Medicine, Doha, Qatar

Abstract

More than twelve years have passed since the publication of the first genome-wide association with metabolomics (mGWAS) in the German KORA study.

With over 50 published mGWAS so far, the largest including over 86,000 participants (http://metabolomix.com), and many more mGWAS in the making, it is time to review what has been achieved so far and where the field is heading.

In this presentation I will cover give a brief historic overview of what has been achieved by the field, with a focus on the complementarities of different platforms and cohorts.

http://www.metabolomix.com/

Watch recording

Questions and answers

?

If you look into the recent findings you have been mentioning, what do you think could be one which would find his way into clinical environment in the near future?

I think it's very much what Claudia already showed. It's about understanding pathways and the more you're throwing in there, the better you understand the pathways. There is a lot of information that flows into developing drug targets, different medications, things like that. And I think there's a lot of flow out, which we don't see directly. We see the output later, if pharma companies bring out new medications, new treatments, it would probably not acknowledge all our studies at that point, but that's really where I think the translation really goes in, and taking off understanding things. Target validation, target identification, and maybe also understanding better treatments and pathways. Polygenic risk and similar concepts are already big topics and we really need these big data sets.

Lessons learned from metabolomics analyses in human cohorts

Prof. (emer.) Dr. Jerzy Adamski

Head of the GAC, Head of Molecular Endocrinology
Helmholtz Zentrum Munich, Germany

Abstract

Metabolomics analyses facilitate understanding of mechanisms underlying homeostasis in health in disease. Metabolomics has been applied in frequent human diseases to generate new hypotheses or elucidate dysfunctionality in obesity, diabetes, cancer, immunological responses, neurodegeneration and even mental diseases.

To provide sustainable resources or allow replication metabolomics studies have to follow strict SOPs in sample collection and storage, quality control and quality assurance during and after measurements, further the meta description of large datasets.

Metabolomics in large cohorts requests some special arrangements in study design, sample randomization and imputing which are different to that in other omics disciplines. Metabolite coverage and sample throughput and data presentation are bottlenecks in metabolomics but there are some strategies how to overcome them.

Metabolomics for Biomedical Research (Book edited by Prof. (emer.) Dr. Jerzy Adamski)

Watch recording

Questions and answers

?

After 40 years research, what has been the most surprising and most important finding of your career?

It was the insight that I will not make any significant contribution to human health if I stay in a field of signal transduction and steroid metabolism. At that time Karsten Suhre and Christian Gieger were asking “why don’t we start doing metabolomics?” This was the biggest and the most important decision I’ve made in the last few years.

Closing remarks

These are my three big takeaways that stand out to me:

1. We're on the edge of a really exciting new era in using metabolomics in population-based studies, to identify disease risk factors and open up powerful new opportunities for personalized treatments;

2. **The value of data lies in how we use and share it.** We have been pointed to tools like JMorp, metabolomix, exposome explorer and omicscience.
   These are the first steps towards sharing harmonized data formats, essential for a more sustainable use of data, and following the FAIR principals of findable, accessible, interoperable & reusable data.

3. Collaboration is key if we are to generate the mega data sets needed for integrated metabolomic and other omics analysis.

Everyone of you can participate in collaborations and make your data accessible to others so we can all work towards a better understanding of health and disease. And this is something the biocrates team is committed to do.

– Thanks to all speakers for being so generous with their time and knowledge, and for giving us some food for thought with their fantastic presentations.

– Thanks to our global audience for joining us on our journey towards more targeted applications of metabolomics.

Dr. Matthias Scheffler
Chief Business Officer

biocrates.com

Virtual event | Pan-Cohort metabolomics –The future of population health playlist

biocrates life sciences ag
Eduard-Bodem-Gasse 8 I 6020 Innsbruck I Austria
Phone +43 512 579 823
Email sales@biocrates.com