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The emerging role of lipidomics in prediction of diseases

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Summary

A recent paper published in *PLoS Biology* reported the application of lipidomics in predicting the incidence of diabetes and cardiovascular diseases in a population cohort. The study is clearly remarkable in demonstrating the role of lipidomics in prediction of diseases and translational research. We believe it comes to an era with quantitative lipidomics.

Lipidomics, as an interdisciplinary research field which greatly relies on large scale analysis of lipid species, emerged in early 2000[1] and has become an important player in understanding a variety of scientific questions, from basic science to translational research[2]. However, its studies on prediction of disease development are still lagged, regardless of great efforts made for biomarker developments and numerous achievements obtained in biomarker discovery. This situation might be changed with a recent report in *PLoS Biology* titled, "Lipidomic risk scores are independent of polygenic risk scores and can predict incidence of diabetes and cardiovascular disease in a large population cohort," from a collaborative study of Lipotype, Lund University, and Twincore Center for Experimental and Clinical Infection Research led by Drs. Chris Lauber and Kai Simons[3].

This study was a continuation of their two previous studies, where separately identified lipid profiles in prediction of type 2 diabetes (T2D)[4] and cardiovascular disease (CVD)[5] by employing one kind of shotgun lipidomics, a high accuracy mass spectrometry-based high throughput approach[6]. The team analyzed baseline plasma lipidomes of 4,067 healthy, middle-aged participants in a prospective case-control Malmö Diet and Cancer-Cardiovascular (MDC-CC) Cohort study recruited from 1991 to 1994, then followed until 2015. In this follow-up period, 13.8% of participants developed T2D, and 22% developed CVD. The investigator quantitatively measured 184 lipid species in the classes and/or subclasses of phosphatidylcholine (PC), ether-containing PC (PC O-), lyso PC (LPC), phosphatidylethanolamine (PE), ether-containing PE (PE O-), lyso PE (LPE), phosphatidylinositol (PI), cholesterol and its esters (CE), ceramide, sphingomyelin, diacylglycerol, and triacylglycerol under the capacity of the approach.

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Competing interests: None.

After lipidomics analysis, the team conducted a variety of statical analyses including Ridge regression-based machine learning modeling on the data. With the Ridge based model, the team iterated 10 training/test rounds using the randomly-split data sets as 2/3 training and 1/3 test, and computed several risk scores (see below) for T2D and CVD incidence during up to 23 years of follow-up. They found the prediction of both T2D and CVD with the risk score computed from lipidomics data (L) is superior to that obtained from the null risk score (N) in which only age and sex of participants were considered, as well as from the polygenic risk score (P). Addition of both null and polygenic scores to the lipidomics risk score only slightly enhances the prediction of T2D, but not CVD, suggesting that the lipidomics risk score is independent of polygenic risk score which was evidenced with the minimal correction between P and L. It should be pointed out inclusion of the clinical risk score (C) calculated from standard clinical and vital measurements (i.e., body mass index, systolic blood pressure, fasting blood glucose, glycated hemoglobin (HbA1c), low-density lipoprotein, high-density lipoprotein, and triglyceride levels) further improved the risk stratification of both T2D and CVD with lipidomics risk score to a certain degree.

After the development of the model, the team clustered the participants into six subgroups based on their lipidomics risk score. They found that, compared to the group averages, the risk for T2D in the highest-risk subgroup was 37%, an increase in risk of 168% with 167 lipid species among 184, and that the risk for CVD in the highest-risk subgroup was 40.5%, an increase in risk of 84% from 157 lipid species of 184. Combination with clinical risk score further improved the risk stratification to 51.0 and 53.3% in the highest risk subgroup for T2D and CVD, respectively. Similarly, the investigators predicted significantly reduced risks in the lowest-risk subgroups with lipidomics risk scores and found that a 77 and 53% reduction in the incidence rate for T2D and CVD, respectively, compared to the average case rates of 13.8 and 22.0%.

There are *multiple important implications* of the reported study by Lauber et al.[3]. *Firstly*, it is clearly remarkable that individuals at high risk for developing T2D or CVD could be predicted many years before disease onset with relatively cheap and fast lipidomic measurement as both T2D and CVD are among the 10 leading causes of death in the world. Currently, the assessment of these diseases largely depends on patient history and current risk behaviors, and standard clinical measurements. *Secondly*, the early prediction of individuals at high risk for developing a disease could allow us to take some precautions such as changing lifestyle and/or dietary pattern, to avoid or delay the onset of the disease. *Thirdly*, lipidomics measurement of plasma samples for populational screening of T2D and CVD in middle-aged individuals becomes possible considering its cost-effective outcomes and outstanding predictivity. *Lastly*, changes of plasma lipidome patterns are usually associated with certain type(s) of metabolic processes. Therefore, lipidomics of plasma samples may provide new insights into the aberrant metabolic changes for potential drug targets.

From the findings of the reported study[3], we could also make the following additional extensions on the role of lipidomics in health and diseases.

First, as well known, the plasma lipidome, counting both content and composition, represents the metabolic consequences of the entire body, thus it should sense the changes of these processes from different organs or reflect the messages via exosomal secretion to a certain degree. Therefore, the approach in the report using plasma lipidomics data to predict T2D and CVD could be extended to study other diseases such as cancer, neurodegeneration, autoimmune diseases, aging processes, etc.

Next, previous biomarker development studies using lipidomics are largely focused on the discovery of specifically-changed lipid class, subclass, or individual molecular species. In contrast to identification of specific changes for biomarker discovery, the report in *PLoS Biology*[3] along with two previous studies from the team[4,5], as well as another previous similar study on prediction of the transition from gestational diabetes to T2D[7] demonstrated a patten recognition approach, in which a lipidomic pattern (or signature) is derived through machine learning analysis of quantitative lipidomics data to predict a subgroup of individuals at high risks to develop a disease. To this end, it would be very interesting and curious to look into the consistent changes of the patterns in some classes, such as PC O-, PE O-, lysoPE, and triacylglycerol as shown in Figure 4 of the report. These consistent trends of risk score quantiles of individual molecular species might be more useful/powerful to predict diseases in the case of T2D and CVD.

Moreover, as the authors of the report[3] emphasized, accurate identification and quantification in absolute molar concentration is essential for successful to achieve the pattern recognition. We fully agree with this assessment[8] since accurate quantification with absolute mass amounts enables us to clearly compute the differential contributions from individual lipid molecular species and make effective pathway/network analysis. In fact, our lipidomics community has been making great efforts towards to this direction[1,9,10].

Finally, regardless of that further confirmation of the lipidomics data with the aid of machine learning analysis from additional studies to demonstrate the feasibility of clinical applications, the role of lipidomics in prediction of diseases is emerging and becomes clear. We anticipate the expanding applications of the approach with other cohort studies and for other diseases.

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