Use of the Quantitative Metabolomic Database (QMDB) for longevity and aging studies

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1 Introduction

Longevity of the human population has increased over the last decades, with most people reaching age 60 or higher (Beard et al. 2016). However, the so called "health span" – the period of life without any disease – has not increased and aging is a key risk factor for diseases and disabilities (Rutledge et al. 2022).

An increasing number of studies are investigating the biology of aging. However, the interaction of many different cellular and biochemical processes as well as environmental factors make it very complicated to untangle the drivers of aging. Many different omics techniques are employed to study this field. Among them, metabolomics stands out as it provides a real-time snapshot of the phenotype, reflecting the effects of genetic, environmental, and other impact factors. This dynamic nature of the metabolome makes metabolomics an optimal tool to study reversible phenomena such as biological aging.

The plethora of targeted and untargeted metabolomics methods have led to limited comparability between studies, impeding meta-analyses to uncover characteristics of aging. biocrates' standardized kits are designed to enable reproducible and quantitative measurements comparable across instruments and laboratories.

The quantitative metabolomics database (QMDB) leverages the absolute concentrations of metabolites measured with standardized biocrates technology. This commercial reference database contains metabolite concentrations measured in plasma samples from healthy adults with MxP® Quant 500 or AbsoluteIDQ p180 kits and provided by contributors from all over the world. The QMDB is described in detail here.

The QMDB contains a high proportion of samples of healthy men and women above the age of 60 (Figure 1), which can serve as a reference group for healthy aging. This makes the QMDB a treasure trove for aging and longevity research.

Hundreds of currently ongoing academic research studies are looking for ways to characterize aging to expand the healthy lifespan and tackle the global rise in chronic disease. Businesses offering consumer tests also increasingly aim to provide individuals interested in improving their lifestyle in favor of a longer, healthy life with meaningful test results and relevant lifestyle advice to increase (healthy) longevity.

For both groups, the QMDB can serve as a reference database to uncover unique traits of healthy aging and compare individual metabolite profiles to typical ranges of an elderly healthy population.

In this application note, we demonstrate how the QMDB can be used to characterize study groups for aging research, as well as an example of how it could be used to assess individual metabolomics measurements in the context of aging.

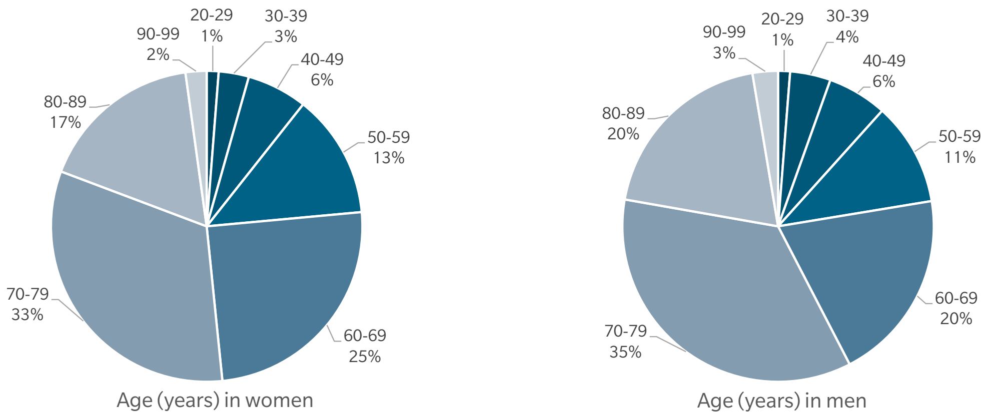

Figure 1. Age distribution of healthy women (n = 1,378) and men (n = 1,210) in the QMDB.

2 QMDB as a reference for longevity and aging studies

The QMDB concentration ranges provide healthy reference data. Two use cases demonstrate possible applications for scientific aging studies.

2.1 QMDB as a reference for control groups

For new studies with a limited number of control samples, the QMDB can be used to assess if these control samples are within the range of a healthy population. The metadata available on the QMDB allow for comparison of metabolite concentration ranges in the general population but also in different sub-populations.

For example, a new study (for the purpose of this application note: "example study") might investigate healthy aging in women and men, using the MxP® Quant 500 kit. To compare concentrations between the control group of the example study and the QMDB across different age groups, data was downloaded for 8 different age ranges separately, using a filter for non-smokers and a BMI below 30, since BMI and smoking are known to have an effect on healthy aging (Ragusa et al. 2025; Radmilović et al. 2023). As there are differences between genders in the context of aging, which are also reflected in the metabolome, it is advisable to download data for women and men separately. Furthermore, data can be filtered for measurements using the MxP® Quant 500 kit only.

The same summary statistics as the ones provided in the QMDB were calculated for the example study to compare the female control groups. Namely, a fold change of the mean and a t-test were used to help identify relevant differences.

For a study on longevity or aging, **age-correlated metabolites are of particular interest**. Figure 2 depicts metabolites with QMDB mean concentrations positively or negatively correlated with age (Pearson´s |r| > 0.95). Most age-related metabolites in the female control group of the example study had mean metabolite concentrations comparable to those recorded in the QMDB. An exception is Cer d18:1/24:1, which was significantly increased in the example study for age groups 20-59. Interestingly, increased Cer d18:1/24:1 has been implicated in cardiovascular disease risk (Hilvo et al. 2020). Apart from the consistent difference for Cer d18:1/24:1, only single instances of age-related metabolite concentration differences reaching significance in the age group 50-59 were detected (for DHEAS and 1-Met-His). It can be concluded that the female control group of our example study represents a healthy control group with slight deviations for a sphingomyelin species.

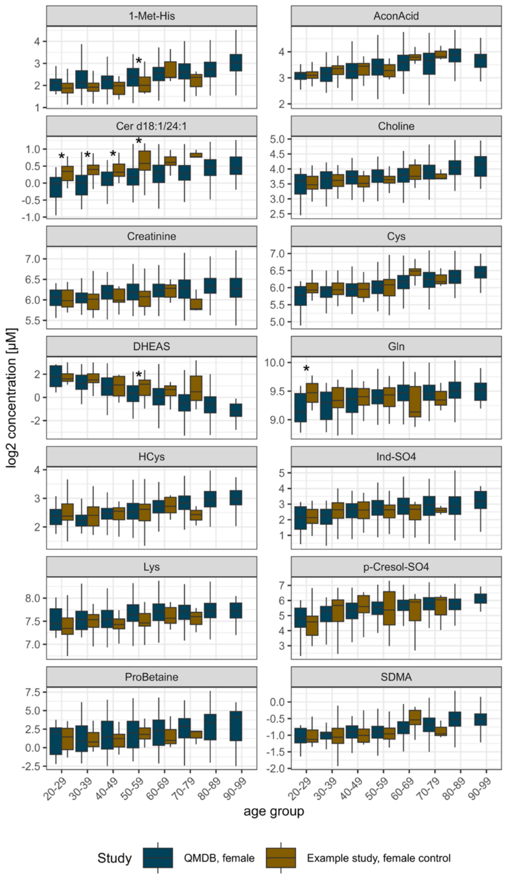

Figure 2. Age-correlated metabolites of the QMDB in women, comparing the QMDB reference ranges and the respective metabolite concentrations in the female control group of the example study. Shown are only metabolites with at least one significant difference between the two datasets. Only metabolites that were detected in > 80% of all samples of a group and more than 3 quantified values per group were included. T-test with FDR correction (Benjamini-Hochberg); *: p.adj < 0.05.

For ages 70-99, the female control group of the example study had less than 3 samples for each age group/gender. For reliable statistics, more samples per group as well as a broader coverage of the different age groups would be needed. In such a scenario, the QMDB can be used as a control group to **evaluate trends before investing more resources in further recruitment for the study**.

2.2 QMDB as a substitute control group

If data collection is not yet completed, or if no control group is available at all, the QMDB might serve as a substitute control group. A possible use case would be a pilot study with a limited number of samples.

As an application example, we looked at the effect of obesity on age-related metabolites. For our “example study 2”, the QMDB was used as a control group for comparison of metabolomics data of obese and non-obese individuals to study the effect of obesity on healthy aging. To generate an appropriate control group for “example study 2”, the QMDB data was filtered for samples of current non-smokers with a BMI below 30 (i.e. not obese, according to the WHO report on obesity and overweight), and data was downloaded split by age group and gender.

A similar approach as for the previous example analysis (Figure 2) was applied to identify significant differences between obese individuals from example study 2 and non-obese individuals from the QMDB per age group. In addition to t-tests, fold changes between means were calculated that can help identify meaningful differences.

Focusing on metabolites that are correlated with age in the QMDB (Pearson´s |r| > 0.95) revealed significantly higher values in example study 2 than the corresponding age group for Cer d18:1/24:1, cysteine, Hex-Cer d18:1/24:1 and PC 28:1 (Figure 3). These metabolites all increase with age in the healthy QMDB cohort. This indicates that the obese group exhibits several metabolic characteristics that are usually found in individuals of higher age groups, which is not surprising considering obesity has been found to accelerate aging (Ragusa et al. 2025).

Unexpectedly, p-Cresol-SO4 concentrations were significantly lower in two of the age groups of obese males compared to the age-matched healthy reference, even though this metabolite generally also increases with age according to the QMDB. This may be connected to p-Cresol-SO4, despite its well-known toxicity, having a beneficial effect on glucose homeostasis and potential for obesity reduction as revealed in a recent study (Zhang et al. 2025).

While not revealing many significant differences yet, partially because the sample numbers in example study 2 are still low (n= 3-6 per gender/age group), this comparison showcases how the QMDB can be used as a substitute control group. The results could support the decision to continue the study and increase the number of samples for the groups. As aging-relevant factors like smoking behavior are also tracked in the QMDB, these could be included in the analysis as well.

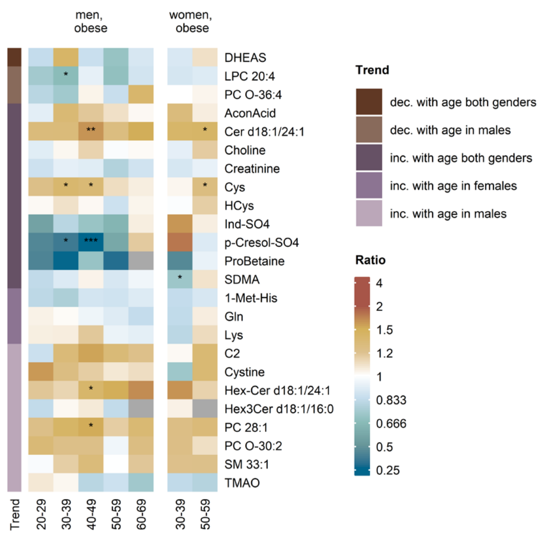

Figure 3. Comparison of age-group correlated metabolites of obese men and women compared to the QMDB (filtered for non-obese individuals). The trend indicates if the mean concentration of a metabolite is increasing or decreasing with age in the QMDB.

3 QMDB as a reference for individual measurements

The QMDB can also serve as a reference database to interpret individual measurements.

In this context, it needs to be acknowledged that the QMDB is intended for research use only and should not be used as a diagnostic tool.

For research purposes, individual values can be visualized in the context of age-related metabolite ranges in the reference population, as visualized in Figure 4. In addition, the k-nearest neighbor to the different age groups can be calculated for individual metabolite profiles using the Euclidian distance. In the example shown here, metabolites were quantified in samples from two female individuals with different health statuses. The non-healthy, obese female was 55 years old and had a metabolite profile closest to the 90-99 age group, i.e., her biological age was much higher than her chronological age, probably at least partially because of increased lipid levels linked to her obesity.

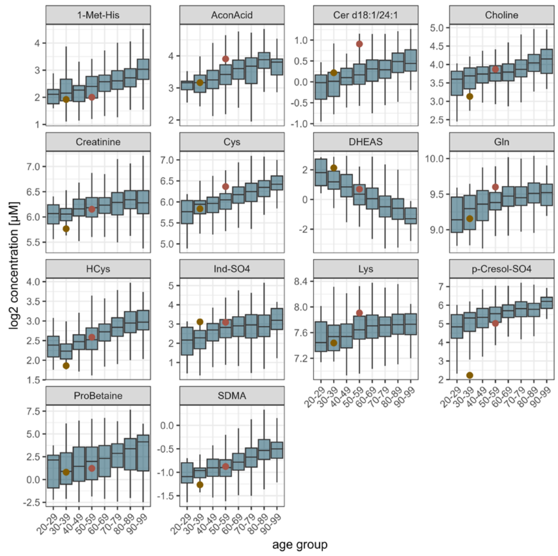

Figure 4. Age-related metabolites and their concentrations in the respective female age groups in the QMDB are visualized as blue boxplots. The red dot represents the values of an overweight female individual, classified as non-healthy. The ochre dot represents the values of a normal-weight female individual, classified as healthy.

The metabolome of the supposedly healthy female (age 32) also showed signs of increased metabolic age as the closest age group was 40-49. Most age-related metabolites were within the reference range, but concentrations of Ind-SO4 were higher than in the reference of her actual age group, indicating that an unfavorable microbiome composition likely contributed to the classification into a higher age group than her own.

4 Conclusion

Recruiting healthy reference groups for aging or longevity research can be challenging. Moreover, gender differences in aging necessitate appropriate recruitment of both women and men.

Making use of the QMDB can facilitate aging research, as it is a powerful and versatile tool when applied as showcased in this application note:

- QMDB enables characterizing an experimental control group as to how healthy and age-appropriate the control group metabolome is.
- QMDB can serve as a substitute control group for pilot studies, before investing more resources in subject recruitment. Here, the QMDB can be used as a control group to estimate effect size for power analyses and to estimate the required sample sizes, facilitating the preparation of grant proposals and applications for human or animal research studies.
- QMDB can be used as a healthy reference database to characterize individual plasma samples, including using concentration ranges of age-related metabolites as a reference for healthy aging.
- QMDB is a great resource for *in silico* studies on aging, revealing metabolites that increase and decrease with age in specific subpopulations identified with the filters available.

5 Outlook

The QMDB currently includes plasma metabolite concentrations from more than 2,500 healthy individuals and continues to grow through community contribution.

Every dataset shared expands the coverage, quality, and utility of the database. By contributing, researchers enable broader scientific impact, and help establish an open, global reference for metabolomics. Contribution of appropriate samples is highly encouraged. Please contact biocrates if you consider contributing your own control results.

6 Bibliography

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biocrates QMDB service for biostatistics

These example analyses already showcase how the QMDB can be of value for studies on aging and longevity. Nevertheless, analyses exceeding the suggested use cases are sometimes precluded by the fact that the QMDB only provides concentration ranges, not concentrations of the individuals these ranges are calculated from.

As a solution, biocrates offers more advanced statistics using the full data of the QMDB within the framework of service projects.

Statistical options offered include:

- Principal component analysis (PCA)
- Partial-least squares discriminant analysis (PLS-DA)
- Interaction analysis between age and certain health conditions
- Classification of metabolite concentrations of individuals in percentiles of the reference population

A multivariate comparison between an experimental control group and the QMDB can provide a helpful overview of general metabolic similarities and differences. Figure 5 shows example PCA plots by age group based on the QMDB and the example study from the above analyses. The marked overlap of 95% confidence ellipses of the new control group of the example study and the QMDB per age group indicates that the general metabolite profiles of the two groups are quite similar for all age categories.

Custom analyses, e.g., a correlation analysis between metabolite concentrations and age, can be mandated as well, supporting individual needs in the context of longevity and aging studies. Additionally, biocrates also offers data interpretation as a service.

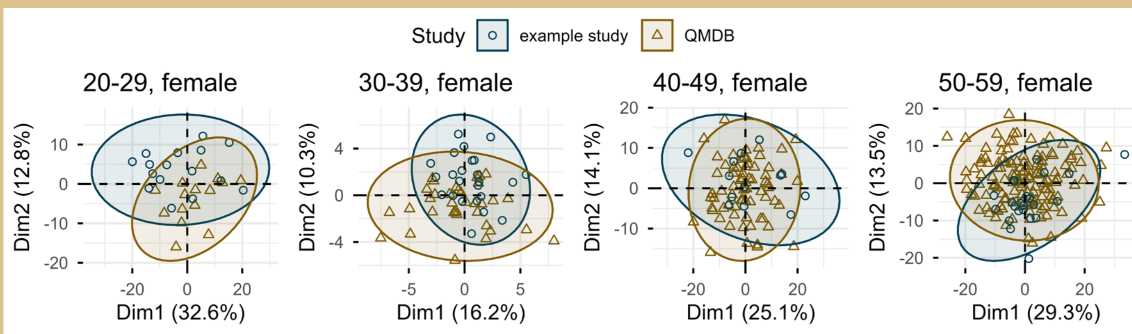

Figure 5. PCA plots of metabolite profiles in different age groups in experimental and QMDB control groups.