



The Impact of Diet on Lab Results and Research Outcomes

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Abstract

Nutritional physiology plays an important role in the functional outcome of studies performed with rodent models. This is important generally in safety and efficacy studies performed to support health claims, but when obesity, type 2 diabetes, or cardiovascular diseases are taken into consideration, it becomes even more important. Several examples are given to illustrate that dietary intervention studies in wild-type mice and rats give relatively small effects compared to in vitro or human studies on parameters such as lipoprotein profiles, biomarkers of inflammation and gene expression responses (P. M. Hovenaars et al., 2012). Generally applied “standard” chow diets usually contain poorly specified ingredients that may strongly vary in composition between batches and between suppliers. Even diets prepared by the same supplier may differ significantly in composition. Since rodents are often used to study functional effects of individual nutrients or groups of nutrients, it is important to use diets that are as much as possible controlled for their composition. This necessity is now widely recognized among researchers employing rodents to unravel molecular mechanisms underlying functional effects of nutritional components. Semi-purified control and experimental diets based on the recommendations of the American Institute of Nutrition for the AIN93 semi-purified rodent diets are increasingly used (Gkiouras et al., 2022). These diets contain purified ingredients of desirable quality, resulting in diets with more defined and controlled composition. Unfortunately, at present there are as many different formulations as there are different research groups. Consequently, a need to further standardize diets has been expressed that would make comparisons of study outcomes easier and would increase efficiency of use of both resources and animals. Despite this need, trying to agree on one formulation for a standard diet has proven to be extremely difficult.

Keywords: Animal diet (chow vs. purified ingredient diets), lab animal species and sex, and time of the year are all variables that affect lab results but are uncommonly reported. Chow and other whole food diets introduce additional uncontrolled variables that can confound a study’s primary experimental hypothesis. This unrecognized complexity is especially true for rodent studies. Some examples of how diet can confound experimental outcomes are presented here, with an emphasis on rodent research. To enhance rigor and reproducibility, diet should be considered an important variable and carefully controlled and reported.



Experimental pharmacology and toxicology studies are usually blinded, randomized, replicate and control for countless experimental variables. However, many such studies, as well as studies of gene-modified animal models of disease, do not control or report a variable that can dramatically impact results, conclusions and their interpretation: the diet fed to the lab animals. Lab animal diets are often the most variable component of preclinical research, notwithstanding the fact that compliance with the good laboratory practice regulation requires standardization of the diet fed to lab animals during pharmacology and toxicology studies (J. Westmark et al., 2022). Rodent models are the most widely used animal models of human disease and drug development yet are commonly fed chow whole food diets. Chow diets introduce numerous uncontrolled variables that can confound a study's primary experimental hypothesis (P. M. Hoevenaars et al., 2012).

1. Introduction to the Relationship Between Diet and Research Outcomes

There is a curious tendency for laboratory confined settings to adopt different policies across institutions, or even within the same institution across departments. One important element, which is either thoroughly ignored or poorly implemented, is the diet of experimental animals prior to research procedures or tissue collection (Gkiouras et al., 2022). Most research on laboratory animals considers other environmental conditions (light cycles, housing numbers, floor space per animal, bedding), but diet's impact on endpoints of lab procedures and experiments has been neglected. In longitudinal studies, compliance with the same dietary regimen is crucial, and it should start with animal's arrival to the lab. In parallel, it is imperative to critically examine the impact of diet on research outcomes prior to study design. This is relevant to all animal models and all possible dietary manipulations used during a study, especially when research involves the analysis of relevant tissues. Hence, diet prior to tissue harvest may alter lab results. A priori consideration of these questions is even more essential for new procedures or research paths, as uncontrolled diet-related artifacts can lead to misleading conclusions. The here proposed checklist of relevant questions may serve as a useful guide.

2. Biological Mechanisms: How Diet Affects Biomarkers and Lab Measurements

The inclusion of diet in the methods section, a best practice in biomedical research, is unfortunately often neglected in studies focused on laboratory measurements. Information on diets prior to diagnoses, treatments, or sample collection in clinical studies and before analysis in animal studies should be included. Likewise, raw data for lab measurements should include information on any diets administered if applicable. Differences in diets can completely alter biomarker measurements, experimental results, and subsequent conclusions, and yet controlled feeding is very rare in most laboratory studies of small animals (Wellington et al., 2019). Diets can have an immediate effect on some biomarkers, while others can take several days or weeks to fully reflect changes in diet. Thus, it is important to



report dietary history and/or administered diets, and inclusion of diet controls is needed for new biomarker proposals.

Numerous metabolites can serve as dietary biomarkers in a variety of biological samples. Most commonly studied are the urinary excretion of dietary sodium, protein, and sugar amounts, validated biomarkers of dietary intake in adolescents. Blood plasma levels of caffeine and multiple trigonelline derivatives can indicate coffee consumption, and two amino acids and five acylcarnitines can indicate tea consumption, both in a controlled diet study in adults. Biomarkers of short-term habitual diet changes in free-living adults have been found using blood plasma profiles of five metabolites indicating a Western diet, and a 15-metabolite signature indicating a prudent diet. Two common fatty acids indicate fish intake in a multi-study analysis of possible confounding factors affecting blood lipid biomarkers. Several metabolites indicating extra-virgin olive oil intake have been found through in vitro digestibility screening and identification in human plasma, and distinguishing intake of long-chain polyunsaturated fatty acid types have been found in a randomized controlled trial of infant formulas.

3. The Influence of Macronutrients on Lab Results

In research settings, it is crucial to consider how the diet of laboratory animals might affect lab results, so the same considerations have been applied to human research subjects. Obvious dietary manipulations will have direct and powerful effects on blood and tissue levels of macronutrients and concentrations of the metabolites that result from their digestion or metabolism. On the other hand, more tightly controlled studies may adjust for such influences by running baseline conditions before the treatment under scrutiny or using matched control groups fed the same diet (J. Kelly et al., 2019). Other aspects of the diet or its macronutrient content can vary between individuals in ways that are difficult to monitor or quantify. Nonetheless, these peripheral influences on research outcomes may be important, especially when considering a population at one extreme of a particular range.

Despite an interest in dietary impacts on health, compliance with dietary controls has not always been thorough. Most studies have been of individuals on a "normal" or "ad libitum" diet, but it is essential to demonstrate what this means for particular cohorts. For instance, the diet of overweight individuals may have a higher relative macronutrient composition of fats or sugars or a higher energy density. Even if adjusting for energy intake, this will not necessarily control for indirect macronutrient ratios as relative fat composition might be 10% in one cohort and 50% in another (A. Koemel et al., 2023). It is also important to note that the same absolute quantity of a macronutrient could have differing effects depending on the wider context of the diet. The same quantity of fat may change lab results one way in a "low"/normal carbohydrate diet compared to a "high"/normal fat diet.



4. The Role of Micronutrients in Research Outcomes

Holding mouse experimental research in a conventional laboratory facility offers a level of controlled biotic, abiotic and social parameters conducive to reproducible results. Nevertheless, there are limitations inherent in any 'closed system' that may skew research results. Most significantly the sources of consumables, especially diet. Commercially prepared laboratory diets often conducted proprietary micronutrient analyses using generally accepted wet chemistry spectrometric methods (Saito et al., 2020) but these figures may not reflect the actual diet fed during ongoing research. Therefore diet should be regarded as a variable, especially regarding micronutrients, and cross-checking pre-purchase analyses with robustness of research outcomes is advised (T. Littlejohn et al., 2023).

Mice were chosen as the model for this experimental research. It was considered outside the technical capabilities of the facility to conduct whole genome transgenic or knockout studies in a higher mammal model. Mice are also low cost, low bioload, small size, rapid breeding and have established laboratory husbandry protocols. Importantly almost 100% of the mouse genome has orthologous human genes. All aspects of this experimental research from mouse husbandry to necropsy were reviewed by and conducted under the approval of the University of Tasmania Animal Ethics Committee to ensure compliance with current Australian standards for the care and use of laboratory animals.

5. The Gut Microbiome: Implications for Research and Lab Tests

In an era where biological research drives medical advancement, the fundamental principles of experimental biology must be embraced and rigorously applied. Such principles include designing experiments appropriate to the question being asked, careful and thorough attention to detail throughout the experimental process, and critical evaluation and understanding of results. Carefully controlling how experimental subjects are treated outside of the laboratory environment, particularly what they eat, is crucial to this process. A systematic review of how dietary choices of laboratory animals, cells, or tissues used in biological research can confound result interpretation was undertaken, focusing primarily on the impact of diet on the gut microbiome. In vivo animal studies and in vitro research using gut microbiome-derived materials, cells, or tissues are emphasized, as they are increasingly common experimental designs in biomedicine (A. Conlon & R. Bird, 2014).

The gut microbiome is the complex ecosystem of bacteria, archaea, viruses, fungi, and other microbes that reside in the gastrointestinal tract of an animal. In humans, the gut microbiome is established shortly after birth and matures during early childhood. Gut microbiome research is a rapidly expanding field, particularly in how the gut microbiome impacts health and disease. Animal models and in vitro systems and research techniques using gut microbiome-derived materials, cells, or tissues are common in this type of research. Because



diet is the main driver of gut microbiome composition and function throughout life, it is a significant confounding variable in this type of research. This lab has been exploring and characterizing the impact of diet on the gut microbiome for many years, including research on how dietary fibers influence health via the microbiome. Drawing on insights and learnings from this research, considerations and guidance on how diet can confound results in gut microbiome research and approaches to minimize this confounding are outlined. How the gut microbiome impacts health and disease, or how to modulate the gut microbiome for health, is the focus of many biomedical research efforts. Experimental design considerations regarding diet that should be addressed in model systems or approaches using gut microbiome-derived materials, cells, or tissues are highlighted.

6. Fasting and its Effects on Lab Results

Most research laboratory work performed on humans involve some form of preparatory instructions to the participants prior to taking the samples. The most common of these preparations typically involve fasting, where in general research participants are instructed to refrain from consuming food and/or drinks for a period of time prior to taking the sample. The general premise behind fasting is that it stabilizes certain metabolic parameters and limits unwanted effects from the diet on the lab results. However, how well fasting works, and whether it is indeed necessary, is seldom evaluated or questioned.

A recent study on how a regular meal affects results from commonly analyzed clinical chemistry analytes found that of 47 analytes, 37 exhibited statistically significant differences after a meal treatment compared to fasting individuals (Lima-Oliveira et al., 2012). These differences were either an increase or a decrease in the analyte concentration ranging from 0.8% to 1352.5%, and, not surprisingly, it was concluded that fasting time needs to be carefully considered when performing these tests to prevent spurious results and reduce the occurrence of affected laboratory errors. It should be noted that this specific study focuses on clinical chemistry analytes usually performed on serum, plasma or whole blood samples. However, the general notion that certain lab tests need to be performed on fasting individuals is in many cases universally applied to all types of tests and sample materials.

7. The Impact of Specific Diets (e.g., Mediterranean, Ketogenic) on Research Outcomes

Diet is a significant variable that may affect the outcome of lab results and other research efforts. Four studies illustrate the impact of diet on serum metabolites and research outcomes even when outside the laboratory setting: the Mediterranean diet, the ketogenic diet, a vegetarian diet, and the impact of 24-hour fasting.

Serum lipids and other metabolites in mice on a Mediterranean diet were studied (J Meidenbauer et al., 2014). Examining serum metabolites in mice fed the Mediterranean diet versus standard mouse chow found a significant effect on research outcomes: profound



differences in the lipids and other metabolites measured. Dietary lipids have a dramatic impact on serum metabolite levels, some of which may otherwise be influenced by other environmental factors.

The impact of a ketogenic diet on C57BL/6J mouse research outcomes was examined. Like the Mediterranean diet, a high-fat ketogenic diet substantially altered serum metabolites and other lab results. Ketogenic diets are gaining popularity in people for weight loss and therapeutic benefits. Dietary therapies have been tested in preclinical mouse models. A ketogenic diet profoundly affected research outcomes in tests of blood-based metabolites, lipids, and hormones. Controlling dietary variables could be especially important in selecting mouse models of dietary therapies used in translational research.

A human study examined differences in the peripheral immune system's response to a vegan versus a ketogenic diet (M. Link et al., 2024). Diets have systemic immunomodulatory effects on the immune response of naïve peripheral T cells. Mechanistically, this effect is driven by diet-induced changes in circulating metabolites, including kynurenine and 3-hydroxybutyric acid, both of which directly target the TCR complex. These findings highlight how controlled dietary interventions in humans can uncover basic physiological principles and advance the understanding of diet impact on health and disease.

A metabolomics approach was used to explore the impact of 24-hour fasting on serum metabolites in C57BL/6J mice. Along with ketone body elevation, global metabolic signatures in several metabolite classes changed that could impact lab readings and research outcomes. Fasting might confound the interpretation of various lab readings and research outcomes that involve baseline reading comparison or data analysis of non-target metabolite classes or compounds.

8. Dietary Supplements and their Influence on Lab Measurements

Dietary supplements are classified as food products by the regulatory agencies, and therefore by law they do not require any premarket safety testing or review. As a result, it is up to the individual consumer to ensure the safety and appropriate use of the supplements. Some manufacturers mislabel their products or include ingredients not listed on the label. There is evidence that some dietary supplements contain undeclared and prohibited substances that can result in positive findings on doping control analysis. Because dietary supplements contain pharmacologically active substances, compassion should be an appropriate recommendation in laboratory animal studies involving the use of dietary supplements. A recent examination of nutritional supplement products purchased in the U.S. found all androgenic-anabolic steroids to be undeclared on the product label (Gabriels & Lambert, 2013). Nine out of ten products analyzed contained one or more of these illegal steroids. In contrast, a larger European survey of dietary supplements marketed for weight loss, muscle



gain, or testosterone booster revealed that only 11% contained banned anabolic steroids. However, for the other classes explored, 41% of muscle gainers or testosterone boosters and 8% of weight loss products tested positive for undeclared stimulants.

9. Methodological Considerations in Studies on Diet and Research Outcomes

While the effect of the diet of laboratory animals on research outcomes is widely acknowledged, this effect is seldom monitored and reported. Preliminary data from a university laboratory indicated that variations in the diet of laboratory animals influenced the lab results and the scientific conclusions drawn from those results. This effect was particularly pronounced in studies involving genetically modified (GM) mouse models.

A patient cohort study prompted a broader investigation into the diet of laboratory and experimental animals and its potential effects on research outcomes (Gkiouras et al., 2022). Mechanistic and experimental studies on diet effects have been conducted over the years, primarily involving laboratory animals. However, as with patient dietary regimes, diets fed to laboratory animals have generally been taken for granted in basic research outside of pharmacological and toxicological studies. This neglect appears to be due to a mixture of methodological complacency, ignorance, and a "deep in the woods" situation for many basic researchers.

Despite a more varied dietary regime for laboratory animals used in preclinical pharmacological and toxicological studies, the most widely used in mechanistic and basic research are one or more commercially available, standardized "lab diets" formulated to contain specified amounts of nutrients, micronutrients, and "bio" ingredients. These diets are presumed to meet the nutritional needs of laboratory animals across the board regardless of species, strain, sex, age, breeding, housing, and environmental conditions. Such lab diets are produced by a handful of commercial companies, and some in-house produced diets are based on these lab diets. Because many basic research laboratories are dependent on the same commercial sources for animal husbandry, diet-induced differences in research outcomes and scientific conclusions should be taken into consideration when interpreting results and scientific conclusions from different laboratories.

10. Challenges and Limitations in Studying the Relationship Between Diet and Lab Results

Diet is a primary intervening factor, not always taken into consideration, that could easily alter results, or raise confounding biases in in vivo laboratory studies or otherwise epidemiological forensic studies based on biomarker analyses. This is especially the case when dealing with the analysis of lipids or other nutrients directly involved in the dietary pattern of the subjects/samples tested (Gkiouras et al., 2022). A great number of scientists have expressed skepticism for the results of RCTs implementing nutrition interventions.



Concerns exist mainly over blinding and the placebo effect, as diet is difficult to blind and specific expectations are inevitably produced either as a placebo, or a nocebo effect. Furthermore, the burden enforced on participants enrolled in nutrition RCTs is great, and the risk for non-adherence increases, the longer a trial continues (Laville et al., 2017). For this, the conduction of pragmatic nutrition trials, even with negative findings has been suggested as an alternative, and specific guidelines were produced to aid nutrition researchers to upscale their study design and reporting. Furthermore, the Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM) approach can also be applied to evaluate the evidence strength on associations between dietary patterns and other outcomes.

11. Case Studies and Examples of Diet-Related Research Outcomes

Experimental diet modulation is regularly employed to investigate the consequences of “omic” perturbation in model organisms or systems. However, alongside desired technical impacts on the system, diet also imposes chemical inputs that perturb baseline-omic datasets. The health focused epidemiological KoMet case-control study explores the influence of diet on systemic metabolite profiling. The study of middle-aged pre-diabetic MetSyn cohorts, affected by lifestyle intervention (diet/exercise), longitudinally-sampled serum- and urine-matrix NMR and LC-MS, generating 45,491 data files/widget-results. Dietary perturbation impacts a chain of data processing steps that convert raw data to comparable/interpretive results ((Kaput & Pontes Monteiro, 2024)).

Sample handling/analysis protocols directly influenced by diet are required consideration. NMR spectral pre-processing removes contributions from variance sources not of experimental interest ((J. Westmark et al., 2022)). NMR quantitation employs column spectral averaging to estimate noise for each spectral region, flagging low regions for exclusion. Experimental conditions controlling sample temperature, pH, ionic strength and concentration can amplify baseline-omic/diet-induced spectral perturbations. These handling nuances impact data quality across disparate orchestrated NMR systems when processing health-cohort like large-scale datasets. Commercial solutions or in-house alternatives employing scripting can automate procedure stringency, aiding multi-system data comparability.

12. Ethical Considerations in Conducting Research on Diet and Lab Results

The publication of research protocols prior to the commencement of a study is considered an important parameter of research transparency, limiting selective reporting bias (Gkiouras et al., 2022). Not all nutrition studies adhere to the protocol publication standard. The CONSORT statement requires registering and reporting the research protocol in a registry. Similar standards also exist for SRs and MAs. Specific standards have been proposed for observational nutrition research based on the STROBE-nut guidelines. Even when protocols



have been published, they are not always followed. Poor reporting quality is also extended in basic nutrition research performed on mice. Meta-analyses of nutrition-related research often fail to adhere to the reporting standards. An important question arising is whether academic journals are responsible for specific inadequacies in nutrition research. The misuse of statistics and their reporting is unethical and should be avoided. Most scientists and statisticians involved in nutrition research appear unaware of the prerequisites needed to produce more robust findings. One responsibility of journal editors is to ensure that published research meets quality standards and scientific integrity. A burden is enforced on participants enrolled in nutrition RCTs, increasing the risk for non-adherence over time. The conduction of pragmatic nutrition trials, even with negative findings, has been suggested as an alternative. More rigorous methodology and reporting are required to promote the science of nutrition. Nutrition affects functional outcomes in studies with rodent models, especially in obesity, type 2 diabetes, or cardiovascular diseases (P. M. Hoevenaars et al., 2012). Dietary intervention studies in wild-type mice and rats show small effects on parameters like lipoprotein profiles, biomarkers of inflammation, and gene expression responses. Standard chow diets have poorly specified ingredients that vary in composition between batches and providers. A 5,000-fold difference in phytoestrogens has been found. Comparing chow diets with semi-purified diets shows differences in digestibility and effective energy intake. Using standardized, semi-purified diets is important for comparing functional effects of different nutrients. Semi-purified control and experimental diets based on AIN93 recommendations are increasingly used, but guidelines allow variation in dietary constituents relevant to health outcomes. There is a need to standardize diets to improve study outcome comparisons and resource efficiency. However, reaching consensus is challenging due to the need for additional analyses in ongoing research. Partners in European research consortia have proposed a common, defined semi-purified AIN93-based reference diet and an experimental high-fat diet.

13. Future Directions and Opportunities for Research in this Field

Additional research and more stringent oversight of diet prior to laboratory analysis would help produce better quality data, ensuring the outcomes are representative of the experimental conditions (Magni et al., 2017). Considering the profound impact of diet on metabolic pathways, gene expression, and physiology, the influence of diet on lab results and research outcomes is an important area for future research that would be beneficial to many fields. In addition to research on the impact of specific compounds in the diet, there is also a role for advocacy regarding the simple practice of ensuring that experimental subjects are on a controlled diet prior to lab analysis. This influence is particularly important for research on preclinical animal models where the subject diet can be controlled. Controlling the diet of animal subjects prior to analysis removes a confounding variable and helps ensure that the outcomes are representative of the experimental conditions, allowing more meaningful



interpretation of the data. Further, quality data is essential to the ongoing interpretation and refinement of in vitro models of disease. For in vitro assays, the diet and habitat of the origin organism should be reported along with other handling protocols. Given the critical influence of diet on lab results and experimental outcomes, it should be considered best practice to control for diet prior to analysis in both in vitro and in vivo studies. An awareness of the influence of diet on metabolic pathways, gene expression, and physiology opens up new avenues of research and technologies capable of further student and modeling progress across many areas of biology, convergence, and precision health.

14.Conclusion

Diet is one of the most important, though often overlooked, confounding factors impacting laboratory data. Recent findings regarding the significant impact of diet on lab data in animals and human research studies highlight the importance of diet control in research design in addition to the traditional controls over sex, age, housing, species, strains, etc. The ad libitum feeding style adopted in most laboratory research may significantly skew the outcomes of robustness of findings and the reproducibility of research results between laboratories. This impact is compounded by the variability of diet compositions and ingredients formulations between laboratories. These findings may provide guidance on future research designs relating to data collection and diet protocols and in the interpretation of past research results (Gkiouras et al., 2022).

Diet is easily adjustable and directly related to laboratory data. Future efforts should focus on developing comprehensive methods to distinguish the biochemical impacts of various diets from those induced by experimentally tested treatments, examining the basic biochemistry of animal/human experimental models under controlled diet conditions, broadly verifying the findings of control diet studies in different experimental models of various diseases, and translating lab data findings into clinical practices and epidemiological studies. To take advantage of diet control in research design and tackle the “robustness crises” and “reproducibility troubles” in laboratory data, necessary changes are needed in the culture of peer-review journals, evaluation systems of research outputs, and funding allocation paradigms.

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