



Building an Epigenetic Database

Reproducibility and orthogonal targets

Ariel Dryden^{1,a}, Eric Zhang^{1,a}, Scott Given^{1,a}, Sage Arbor^{1,b}

¹Marian University College of Osteopathic Medicine - Indianapolis, Indiana, ^aMedical school 3rd year student , ^bFaculty P.I. Biochemistry PhD

ABSTRACT

Odds ratios quantify how strongly the presence or absence of a property correlates with the presence or absence of another property in a given population. In the biomedical sciences they are an effective way to investigate the effectiveness of medical interventions towards desired outcomes and the strength with which certain factors influence the risk of a particular disease. Our goal is to collate the significant amount of data that has been published regarding interventions and risk factors using odds ratios into a single database that can be used by the public to compare their effectiveness and importance in influencing desired outcomes in medicine.

INTRODUCTION

While a tremendous amount of data on the effectiveness of medical interventions and the influence of risk factors on patient outcomes has been published, comparing and contrasting them across a wide breadth of topics can be difficult. We believe that there is a space for the creation of a database that allows healthcare providers and researchers to more easily compare the changes these factors have on patient outcomes.

Our metric of comparison is the odds ratio. An odds ratio quantitatively describes the association between a property A and a property B. If the odds ratio is greater than 1, then having property A raises the probability of having property B. Likewise, if the odds ratio is less than 1, then having property A lowers the probability of having property B. It is calculated by assessing the odds of having A for an individual who has B, the odds of having A for an individual who does not have B, then dividing the latter by the former. It is similar to the risk ratio, which is computed using probability rather than odds. Compared to the risk ratio, the odds ratio is more often able to be calculated from the available data. Because it is relatively easy to compute and analyze binary properties, odds ratios provide a useful metric by which the influence of many different medical interventions and risk factors have on a desired clinical outcome can be compared on a quantitative basis.

The goal of our current research is to begin collection of data for the database while also investigating methods by which published research can be reliably and reproducibly collected and interpreted to be put into the database. Our system involves the use of multiple contributors working independently to collect and interpret research results and using online electronic resources such as Google Sheets to verify and compare the data gathered by different researchers. To ensure consistency of terminology, we used MeSH (Medical Subject Headings) terms, a hierarchy of terminology used by the National Library of Medicine to organize scientific literature. This also facilitates database search due to the nested hierarchy of terms.

FIGURE 1 : CRITERIA FOR COMPARISON AND DUPLICATION

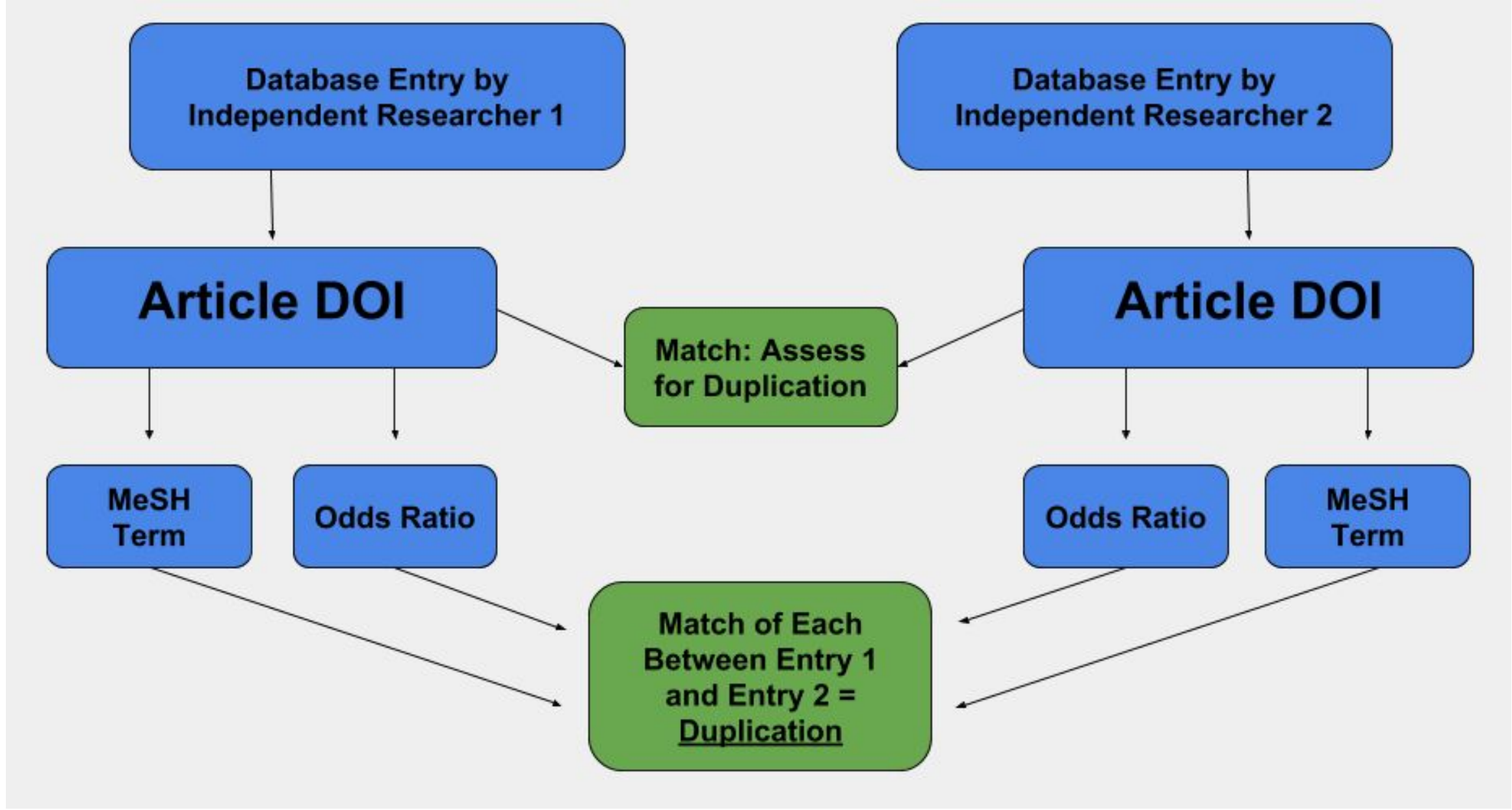


Figure 1: Flow chart showing the process by which individual entries were compared, as well as the criteria that was required to be met to be considered a duplication.

FIGURE 2 : MeSH TERM TREE STRUCTURE

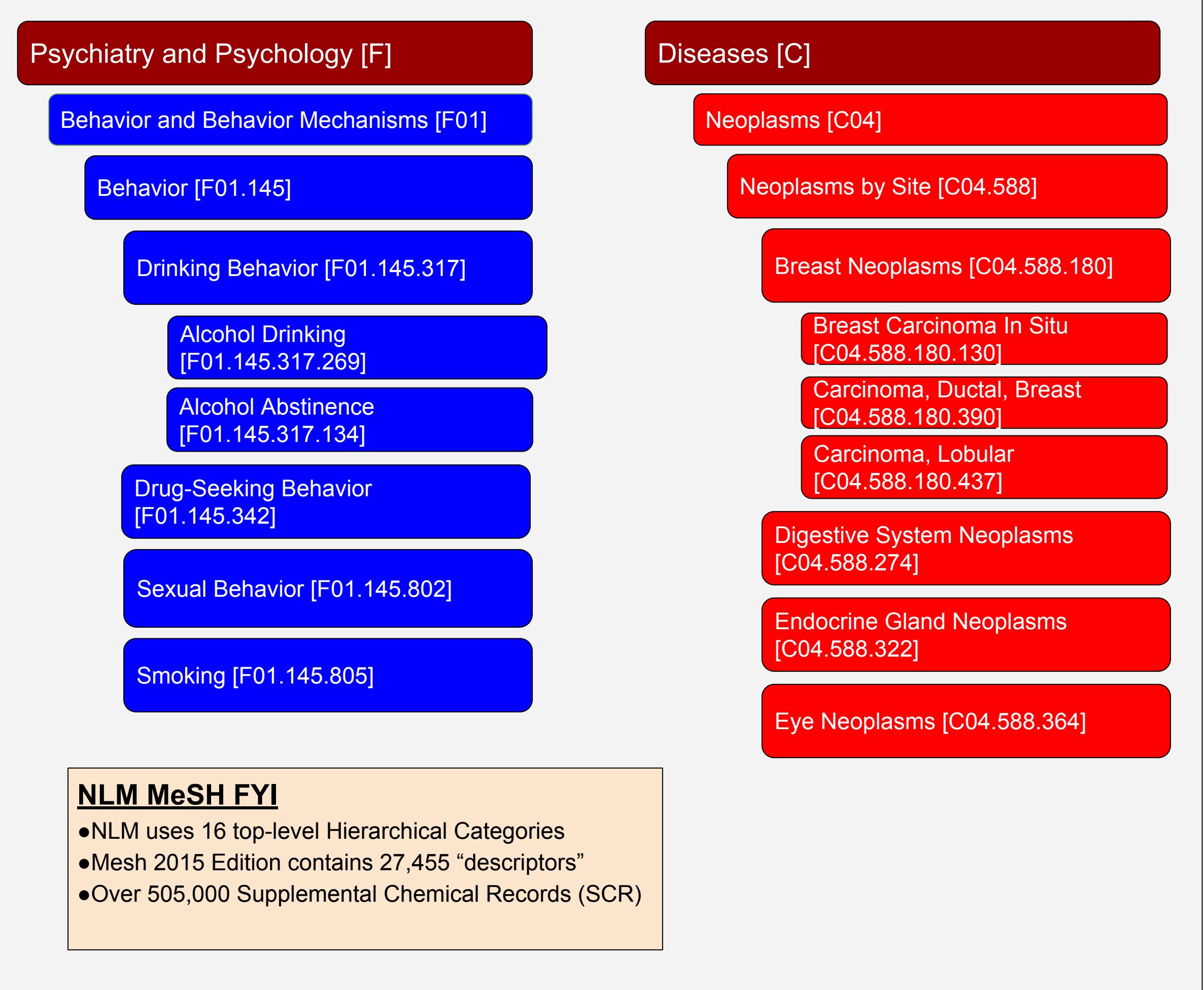


Figure 2: MeSH terms (Medical Subject Headings) are hierarchical vocabulary developed and utilized by the National Library of Medicine to organize scientific literature and terminology. The chart above displays the hierarchical organization/categorization of both a behavior (left side) and a disease process (right side).

ABBREVIATIONS

OR = Odds Ratio
CI = Confidence Interval
DB = Database
MeSH = Medical Subject Headings

RESULTS

Table 1:

Number of papers	65
Number of contributors	11
Average papers per contributor	11.8
Min and max papers per contributor	1-44

Figure 1a: Literature input to database reproducibility

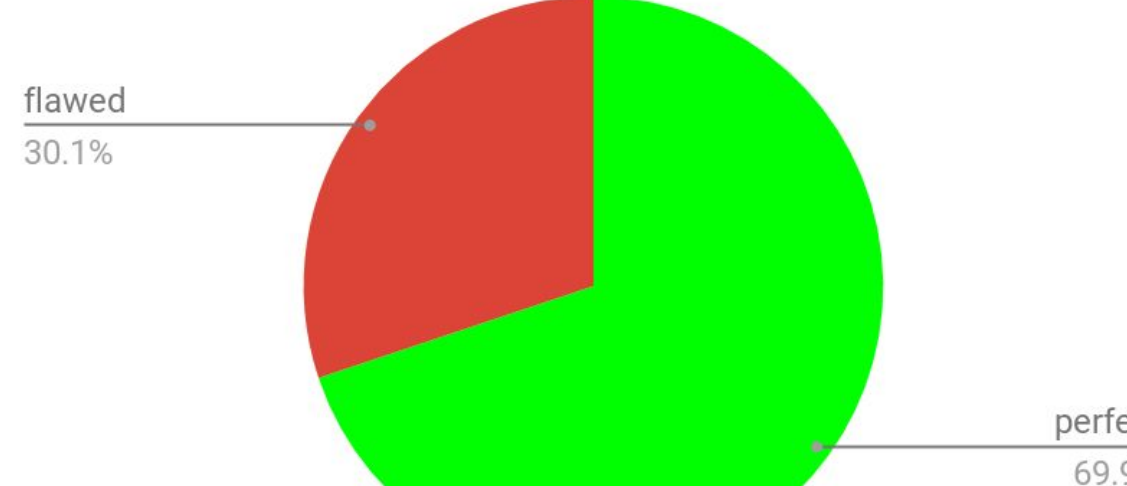


Figure 1b: Fraction of literature review completion

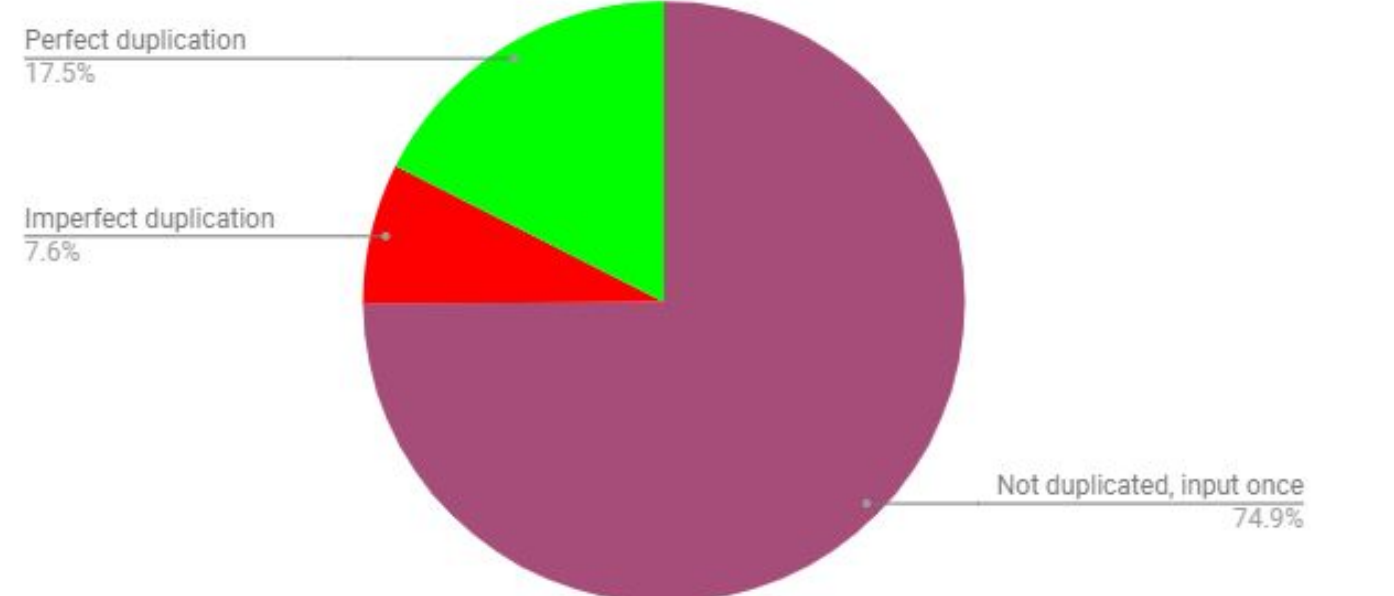


Figure 2:

Number of Inputs and Average Odds Ratios

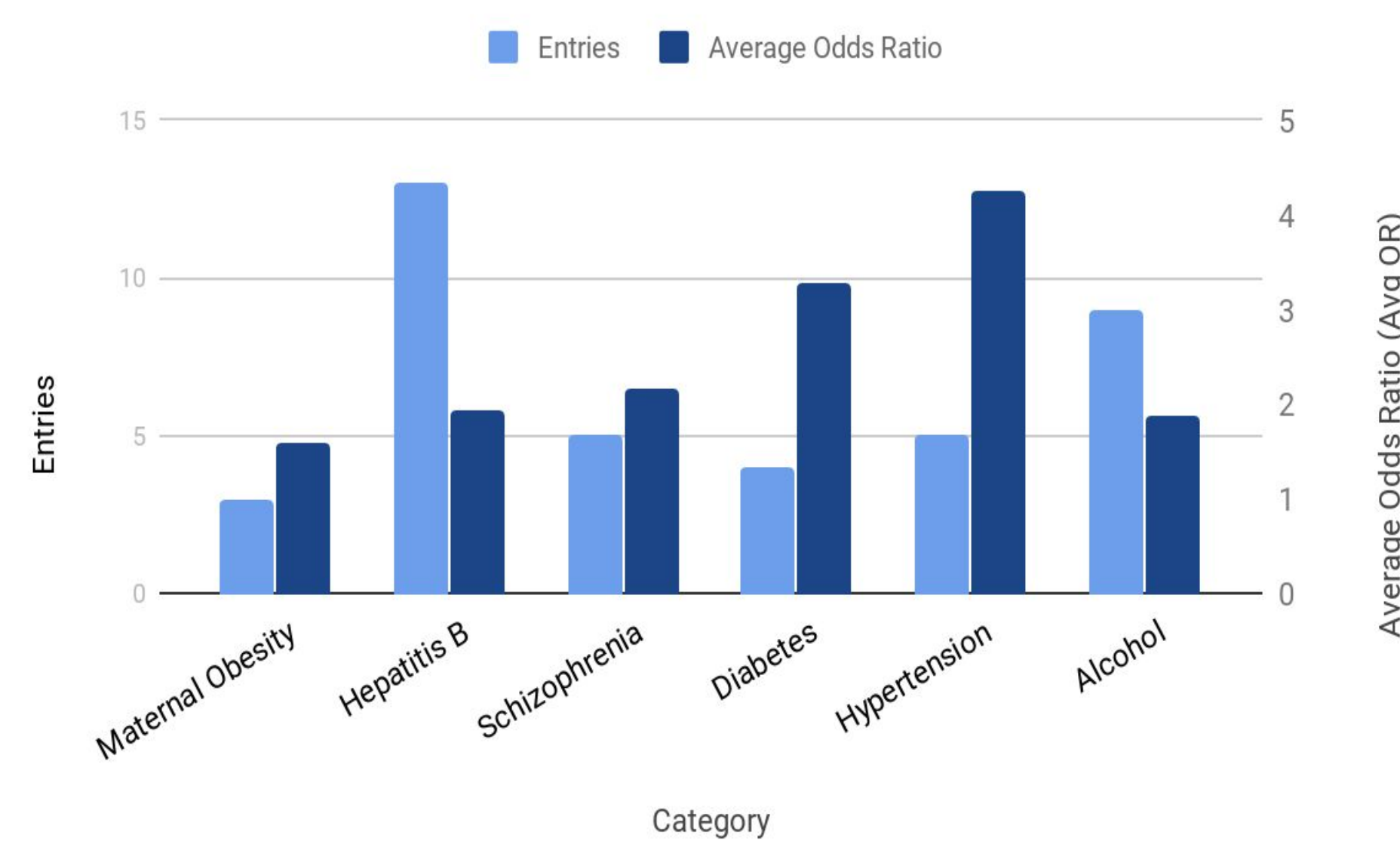


Figure 3a: Change in Breast Cancer Risk with Various Factors

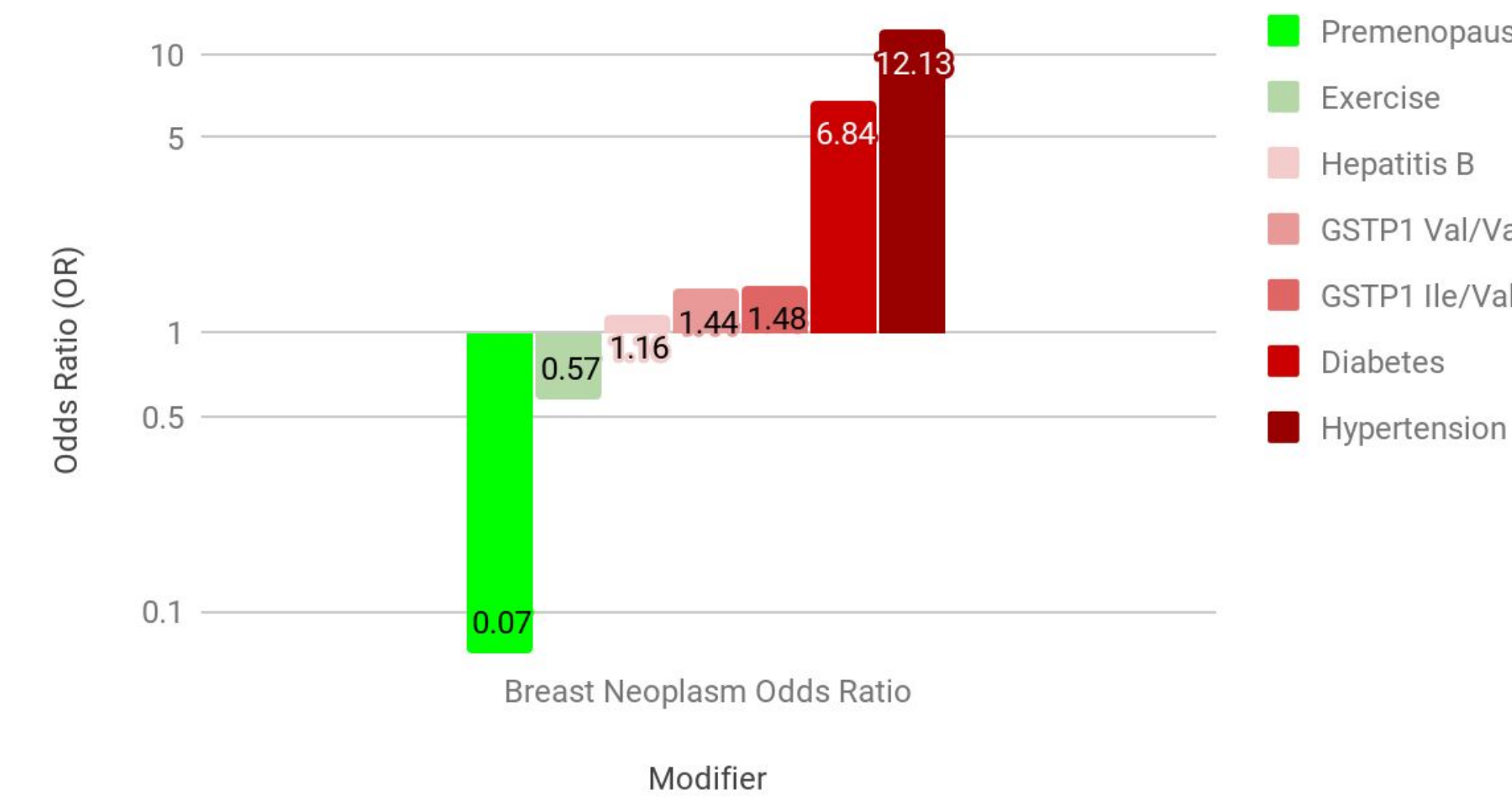


Figure 1 = Table summarizing data in database. # papers, # contributors, Avg min and max #papers/contributor, % duplicated. Figure 2 = Bar graph of main categories inputs. Exercise, diet, sleep, smoking, diabetes. Two y-axis, # publications and odds ratio. Figure 3a, b = Mock searches with real data. Rank ordering interventions.

MATERIALS & METHODS

Database Design, Layout, and Access:

Google Spreadsheets was utilized to ultimately create a single database of compiled epigenetic information from various scholarly works. A total of 3 Google Spreadsheets with different levels of access were created in order to maintain individual researcher independence while simultaneously compiling all information into a centralized database. These sheets are described as follows:

- The Individual Database.** Multiple documents were created and assigned to each individual researcher for independent data entry. This independent data entry process is detailed below under "Independent Researcher Data Entry". Each document was only accessible by the individual researcher, but the Principal Investigator had access to all documents.
- The Master Document.** This is the "Centralized Database" only visible to the Principal Investigator. The Spreadsheet was essentially a large compilation of the data recorded by all independent investigators within their respective individual documents.
- The Done List.** This document was accessible to all parties involved (all researchers and Principal Investigator). A form in Google Spreadsheets was utilized to keep track of literature review/data entry progress. This spreadsheet contained a list of selected research articles, as well as a visualization and documentation method in which researchers could stay up to date on which literary works 1) had yet to be reviewed, 2) were in the process of being reviewed, or 3) had been completed. This allowed researchers to remain both independent and informed throughout the process.

Independent Literature Review Process:

Medical students worked independently to conduct literature-review style research of a series of 69 published journal articles related to epigenetic modification. Zotero reference management software was utilized to maximize organization of literary sources during this process. Each article was to be reviewed and the data recorded a total of 2 times--each by different student researchers working independently. The aforementioned "Done List" was utilized to keep track of literature review/data entry progress. This allowed researchers to remain both independent and informed throughout the process. Each independent researcher was tasked with searching for and documenting key metrics within the literature; the most important for this particular project being the odds ratio. Following a detailed review of each assigned article, the researcher would record these key metrics within an individual spreadsheet database only accessible to them.

Independent Researcher Data Entry:

Student researchers then independently entered key metrics into the aforementioned drop down-style individual database located within Google Spreadsheets. Following data entry, information from all independent databases of each researcher would be visible to the Principal Investigator within the "Master Document."

MeSH--Medical Subject Headings (Information gathered from www.nlm.nih.gov):

The various inputs (independent variables) and outputs (dependent variables) were organized and standardized by utilizing MeSH--Medical Subject Headings to ensure consistency of terminology. MeSH Terms are a form of controlled subject vocabulary created by the United States National Library of Medicine which are utilized to index life science research content. The biomedical terminology is organized in a hierarchical fashion as follows: Mesh Descriptors are organized into 16 categories. Each of the 16 categories are then subdivided into 4 sub-categories. Within each sub-category, descriptors are further organized in up to 13 hierarchical levels from most general to most specific. A series of numbers often follows the descriptor term, indicating its location within the MeSH "Tree". These lists of terminology are often described as "trees" given their branching hierarchical structure. An example can be visualized in Figure 2.

Methodology for Data Analysis:

Google Spreadsheets was used to search the database and analyze the data. Each entry was assigned a paper by its DOI and where two entries from the same paper had the same MeSH terms and odds ratio, it was considered to be a duplicate. The raw database was then pruned of all incomplete duplications in order to produce the final database. Entries with the same odds ratio and DOI were considered to be attempted duplications, entries where all data was identical were considered to be perfect duplications, and entries with the same odds ratio and DOI but with different other variables were categorized as imperfect duplications. The ratios of these can be seen in Figure 1a and 1b. The final database was used to produce results of mock searches by counting the number of entries under a given MeSH term and terms within a given term's tree structure. For example, entries for both "ER+PR+ Breast Cancer" and "ER+PR- Breast Cancer" would be included in a search for "Breast Neoplasms".

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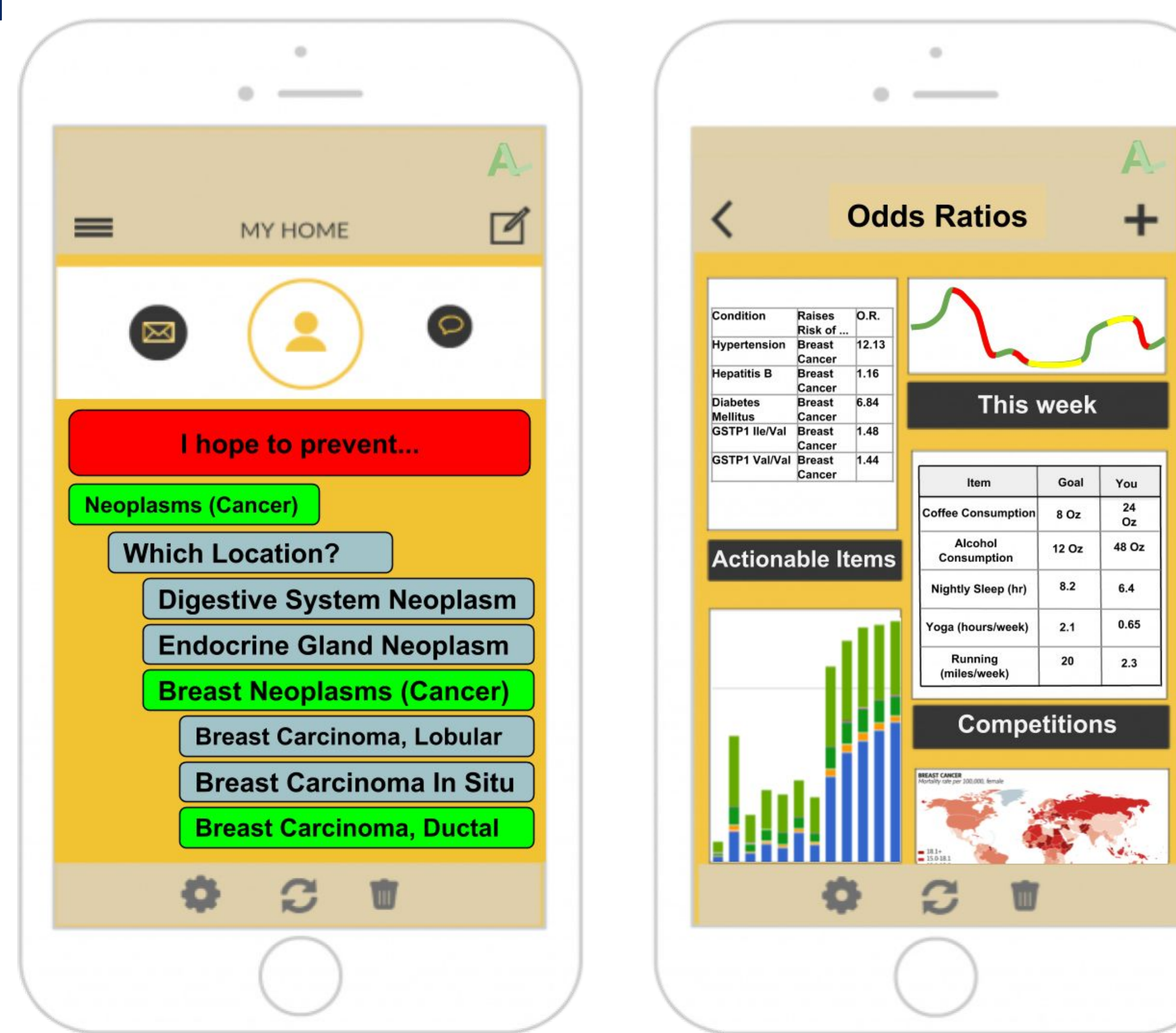
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Introduction: What is MeSH? PubMed Online Training. National Institutes of Health - U.S. National Library of Medicine.

More papers were input in the epigenetic database than are shown for data on this poster.

FIGURE-4 : MOCK-UP OF SMARTPHONE APP



CONCLUSION

Our results demonstrate the potential for our method of independent contributors collecting data from published papers, sorting it under MeSH terms, and using publicly available software from Google Docs to verify results between researchers by cross-checking for duplicated data from different contributors. The prototype database generated in this experiment was searchable using Excel and Google Sheets, with the results of mock searches using real data being displayed above in figures 2-3b. However, the percentage of successful duplications was lower than desired (69.9%), indicating problems with our methodology. Reasons for this may include inadequate standardization of techniques between contributors, an incomplete MeSH term database, and an insufficient number of contributors per paper. Additional training of contributors at the start of data entry could improve consistency in paper interpretation, and inclusion of additional MeSH terms in the database may improve consistency by allowing for increased specificity in term selection. Future experiments may increase the number of contributors assigned to each paper from two to three, to increase the number of successfully duplicated entries.

CONTACT INFO

Sage Arbor
Assistant Professor of Biochemistry
Marian University College of Osteopathic Medicine
3200 Cold Spring Rd, Indianapolis, IN 46222
www.marian.edu/research/sage
Arbor@marian.edu
November 9th Marian University - Research Day

FIGURE 5: PERFECT REPLICATION DATA

Num Rows	input	input min	input max	output	Output Type	output min	output max	Output Unit	Risk	measure of Risk	Lit DOI
1	Alcohol Drinking	2 [F01.145.317.289]	1	1 yes/no - binary (10)	Pepic Liver Neoplasms [C04.588.227.703]	number	1	yes/no - 1 binary (10)	2.20	10.1111/jgh.12805	10.1097/ALN.0000000000000000
2	Angina Pectoris	2 [C14.588.467.187]	1	1 yes/no - binary (10)	Cataract [C11.510.245]	number	1	yes/no - 1 binary (10)	1.46	9	10.3349/jgm.2015.56.6.166
1	Anti-Inflammatory Agents, Non-Steroidal	2 [D01.505.496.196.300]	1	1 yes/no - binary (10)	Pepic Liver Neoplasms [C04.588.227.703]	number	1	yes/no - 1 binary (10)	2.00	10.1111/jgh.12805	10.1097/ALN.0000000000000000
2	Ashtoria [C05.550.114]	1	1 yes/no - binary (10)	1	Cataract [C11.510.245]	number	1	yes/no - 1 binary (10)	1.54	3	10.3349/jgm.2015.56.6.166
2	Ashtoria [C05.127.106]	1	1 yes/no - binary (10)	1	Cataract [C11.510.245]	number	1	yes/no - 1 binary (10)	1.30	3	10.3349/jgm.2015.56.6.166
2	Caffeine	2 [D01.512.463.170]	1	1 yes/no - binary (10)	Colitis, Ulcerosa [C06.405.469.432.2.46]	number	1	yes/no - 1 binary (10)	0.61	10.1111/jgh.13094	10.1097/ALN.0000000000000000
2	Candida Sensitivity	2 [C14.587.801]	1	1 yes/no - binary (10)	Cytic Neoplasmy, Ischemic [C14.587.801]	number	1	yes/no - 1 binary (10)	2.70	01533	10.1097/ALN.0000000000000000
2	Cataract	2 [C11.510.245]	1	1 yes/no - binary (10)	Cytic Neoplasmy, Ischemic [C14.587.801]	number	1	yes/no - 1 binary (10)	5.62	01533	10.1097/ALN.0000000000000000
2	Celiac Disease	2 [C14.482.603.200]	1	1 yes/no - binary (10)	Parkinson [D17.880.033.070]	number	1	yes/no - 1 binary (10)	1.72	10.10386/j.2017.6.161	10.1097/ALN.0000000000000000
2	Cholesterol	2 [D01.505.466.170]	1	1 yes/no - binary (10)	Cortic Disease [C06.405.469.432.5.05]	number	1	yes/no - 1 binary (10)	3.89	10.1111/jgh.13094	10.1097/ALN.0000000000000000
2	Contraceptives, Oral	2 [D07.505.496.875.300]	1	1 yes/no - binary (10)	Colitis, Ulcerosa [C06.405.469.432.2.46]	number	1	yes/no - 1 binary (10)	1.30	00015	10.1097/ALN.0000000000000000
2	Contraceptives, Oral	2 [D07.505.496.875.300]	1	1 yes/no - binary (10)	Colitis, Ulcerosa [C06.405.469.432.2.46]	number	1	yes/no - 1 binary (10)	1.30	00015	10.1097/ALN.0000000000000000
2	Contraceptives, Oral	2 [D07.505.496.875.300]	1	1 yes/no - binary (10)	Colitis, Ulcerosa [C06.405.469.432.2.46]	number	1	yes/no - 1 binary (10)	1.30	00015	10.1097/ALN.0000000000000000
2	Depression	2 [F01.145.128.393]	1	1 yes/no - binary (10)	Rheitis, Allergic [C06.405.469.432.2.201]	number	1	yes/no - 1 binary (10)	1.25	5	10.10386/j.2017.6.161
2	Dermatitis, Atopic	2 [C17.800.174.150]	1	1 yes/no - binary (10)	Cataract [C11.510.245]	number	1	yes/no - 1 binary (10)	1.50	3	10.3349/jgm.2015.56.6.166
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Autism Spectrum Disorder [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Breast Neoplasms [C04.588.180]	number	1	yes/no - 1 binary (10)	6.84	10.77620/j.2017.6.161	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Cataract [C11.510.245]	number	1	yes/no - 1 binary (10)	1.78	3	10.3349/jgm.2015.56.6.166
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
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2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Diabetes Mellitus	2 [C18.246]	1	1 yes/no - binary (10)	Intellectual Disability [C06.405.469.432.2.113]	number	1	yes/no - 1 binary (10)	2.05	10.1543/jgm.2015.2206	10.1097/ALN.0000000000000000
2	Di										