

**Systematic review of the statistical scope used in studies based on skeletal muscle
autophagy and exercise**

By Diane Brownlee

Abstract:

Skeletal muscle reaction to exercise is an essential area of research due to its ongoing prevalence in disease research and general health. It is well documented that under exercise conditions, biogenesis and autophagy increase. One main component of this pathway are lysosomes, the essential cellular clearance machine. Statistical analyses used to analyze these data have been sustained over the years. The objective of this systematic review is to compare and contrast the different methods used for analyzing data in molecular exercise physiology. Upon investigating the research papers the majority of the papers used either a t-test or an ANOVA as their primary statistical analyses, used 41% and 64% of the time, respectively. All other statistical tests were used a maximum of 9% of the time. Another trend that was evident was the increased utilization of post hoc tests in the more recent papers compared to earlier papers. This could provide interesting evidence into the credibility of the results reported and provide more insight into the research in molecular exercise physiology.

Background and Introduction:

Skeletal muscles have an amazing ability to adapt to energy demands. Biogenesis and autophagic processes are in place to allow the muscles to maintain a healthy homeostasis while adapting to these changing requirements. During contractile activity there is an increased

necessity for energy and therefore mitochondrial biogenesis will take place in order to respond to this increased need (1, 2). Maintaining cellular homeostasis during changing requirements for ATP productions requires the cellular process of autophagy and biogenesis. These processes will occur through the activation of fission and fusion (3, 4). In addition to increasing mitochondrial content through biogenesis, the mitochondria also move continuously throughout the cell to allow for all energy demands to be met (7). Repeated bouts of exercise, such as training, have been found to increase the content of mitochondria in skeletal muscles by biogenesis. This rapid adaption allows for increase energy demand, and with training will increase their oxygen and ATP flux capacities (8).

In addition to the biogenesis process, cellular homeostasis also requires autophagy. Autophagy is a lysosomal-mediated cellular clearance mechanism that is always ongoing at low levels in the cell (9). This fundamental catabolic system allows cellular compartments to rid themselves of harmful or dysfunctional products, abnormal protein aggregates and pathogens. Additionally, this process recycles the components of the dysfunctional products and provides the cell with building blocks, energy and nutrients (10). During autophagy a double membrane vesicle, termed an autophagosome, sequesters the targeted organelle or component and a portion of the cytoplasm, and transports the vesicle to the lysosome (11, 12). Once at the lysosome the autophagosome and lysosome fuse to form an autophagolysosome and the internal components are degraded (13). Autophagy is active in almost all mammalian tissues, and serves as a quality control process and allows for the optimal function of the tissues. Any alterations in this pathway could cause harmful effects such as cancer, neurodegeneration, aging and heart disease (10).

This systematic review examines the effect of exercise on muscle and autophagy. The purpose of this review is to appraise the current literature and examine the different statistical

analyses used in scientific papers that were written between the years 1978- 2014. The following questions will be addressed in this systematic review; 1. What statistical tests are most used in this field of exercise physiology, 2. Where these tests were most prominently used and, 3. How the use of post hoc tests and number of tests change over the years.

Methods:

Study Selection Process

A search was completed using ISI Web of Knowledge for articles associated with lysosomes in skeletal muscle. One search was performed in September 2014 on this topic resulting in 166 articles. Search terms used were (exercise*) AND (lysosome*) AND (muscle*). These search terms were refined to increase the specificity and investigate the statistical tools that were utilized by these authors. The first stage limited the articles selected to only articles that conducted research, removing all reviews, notes and handbooks (127 articles remained). In the second stage of refinement, articles were screened and all studies that were not specific to the search terms and was not relevant to exercise in muscle were removed (122 articles remained). Following these stages of refinement the articles were screened in the third stage to remove all studies that did not utilize statistical analysis. These studies consisted of case studies or observational studies and did not compare groups using statistics (74 articles remained). A PRISMA flow diagram was generated outlining the publication selection process (Fig. 1).

Data collection and analyses:

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Data for the statistical tests used, subjects, sample size and location were extracted from the articles methods, tables and figures. Studies varied from observational case studies to laboratory methods in the articles analyzed. This information was then placed in a spread sheet where the information was compiled in annual summaries as well as individual article summaries.

Results:

This compilation of papers showed that the majority of the papers were written and completed in Finland or USA, 23% and 22% of the papers respectively (Figure 2). These papers showed that 45 out of the 74 papers that used an ANOVA in their statistical analyses used in almost every country that published papers in this area of research. The second most used statistical analysis was a t-test, 30 out of 74 papers used this test. All other tests and post hoc analyses were only used in 7 or less of the countries for each test (Figure 3). Next, trends involving the number of authors were analyzed; the average number of authors for all the papers analyzed was 6.08 authors. The number of authors was compared with the number of citations and there was no correlation or trends were seen. Additionally, the number of statistical test used per paper was not correlated with the number of authors writing the paper. When analyzing the average number of statistical tests that were used per year to investigate the trends of tests used per year, there was no increase in the number of tests that were used in the publications per year (Figure 4). Additionally, the frequency of post hoc tests used annually was examined (Figure 5). It was shown that there is a trend to increase the frequency of post hoc tests used per year as time went on. Interestingly, This increase in post hoc tests was not accompanied by a change in the

types of tests that were most frequently used, ANOVA and t-test, it was also not accompanied by an increase in the number of tests used. Though the post hoc analyses changed over the years there was not change in the average sample size of 14.5, there were a few exceptions to this average that had sample sizes around 150 samples but overall, over the years the average has not changed. The large sample sizes varied from rodent samples to human case studies.

Discussion:

In the last decade there has been an increase in studies published concerning lysosomal and autophagic response in skeletal muscle. Though systematic reviews in this specific molecular area are not frequently completed, this statistical systematic review will provide novel information and a new insight into the components of this research area. This is a useful area of research as these study results can aid in therapeutic and preventative measures for diseases caused from or that are the cause of muscle disuse and wasting (23, 44, 48, 53, 58, 67, 68, 69, 71, 76). This is important to investigate due to the aging population suffering from sarcopenia and other muscle related diseases.

Along with the increase in publications there is also an interesting trend seen in the statistical analyses that are done with these studies. The average sample size of all the studies published is 14.5 samples. The small sample size would explain why statistical tests like a t-test or ANOVA were used most frequently. T-tests are used in a wide variety of ways, and work with the means of a sample group; so, it could work with a smaller sample size, as seen in these studies. Additionally, it was shown that post hoc tests have been used more frequently in the more recent years than before; this was not accompanied by an increase in statistical tests done

per study, meaning that post hoc tests became incorporated into the standard number of statistical tests completed in the more recent years. Post hoc tests are very useful in researching trends and relationships between experimental groups. Additionally when using statistical tests like the ones seen in this study for example, ANOVA and t-tests, a post hoc analysis will aid in the prevention of type 1 error. Having appropriate sized samples groups and prepared and controlled treatment groups allows for these experiments to be completed accurately and feasibly. Its important for these studies that can have significance in important medical fields involving diseases and aging population. Completing post hoc tests and the appropriate statistical tests is something that has been increasing in this field recently. This novel insight into the statistical analyses in this area will help to elaborate the essential and useful tests used in this field. It's evident in the methods that are commonly used in exercise studies that t-tests and ANOVAs are usually sufficient to answer the questions that are set out by the researchers.

Conclusion:

After analyzing the publications that were relevant to autophagy and skeletal muscles it was apparent that the majority of the studies produced were in Finland and the USA. This trend has been carried over from 1978 to the present day. In addition to where the studies were published from it was also important to investigate the types of statistical tests that are used in this field of research and how the tests used changed over time. Though there was a wide variety of tests that have been utilized in this field, the majority of the studies used either a t-test or an ANOVA to analyze their results. It was found that there was no trend seen in the amount of tests that were used per study, but there was an increase in post hoc tests. As the field evolves it

became more important to have sound reproducible data, therefore ensuring that the type 1 error is minimized and relationships and trends between sample groups are solid, post hoc tests have been used more frequently in recent studies.



PRISMA 2009 Flow Diagram

Identification

Screening

Eligibility

Included

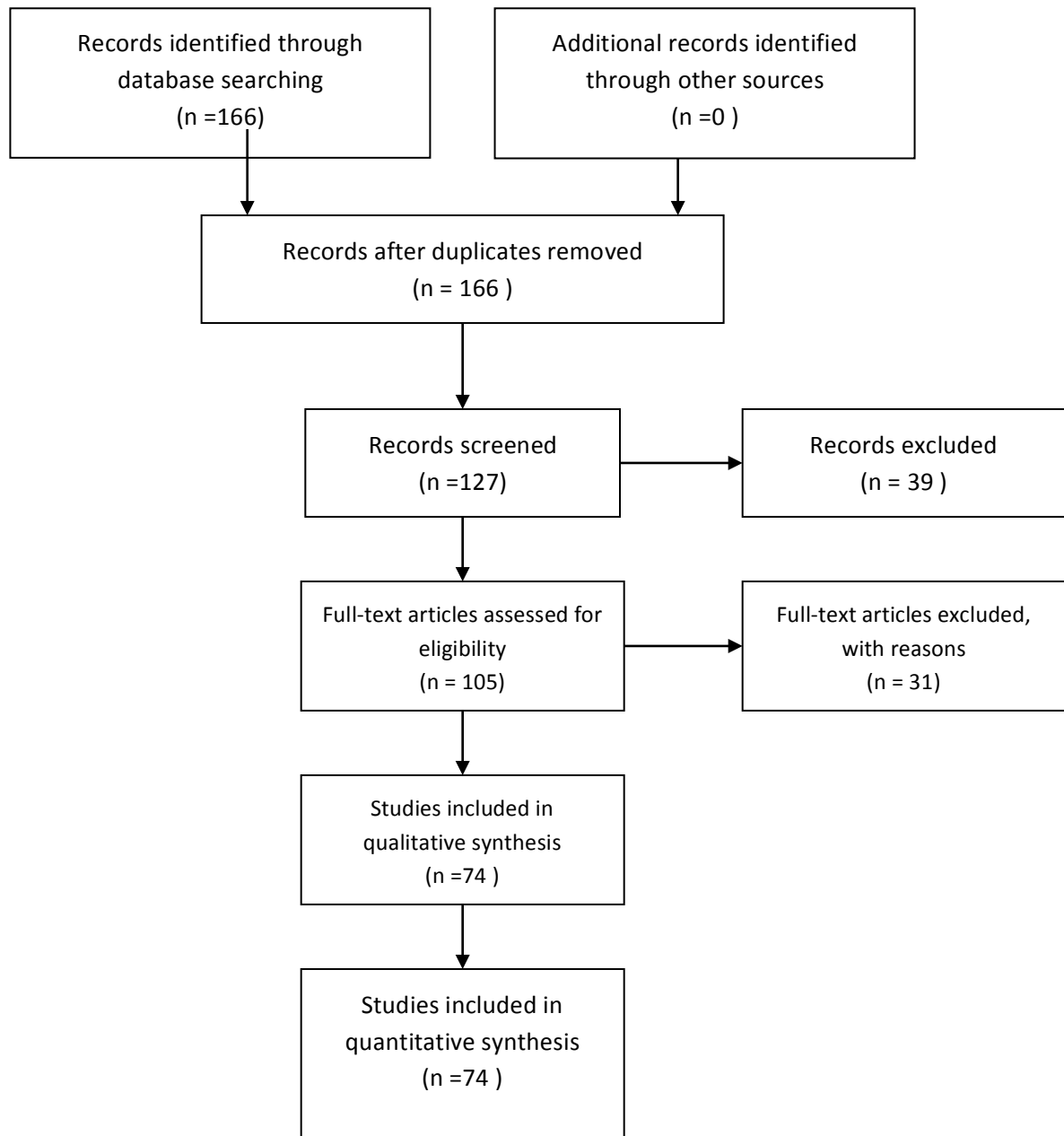


Figure 1: PRISMA diagram describing the protocol used for the systematic review.

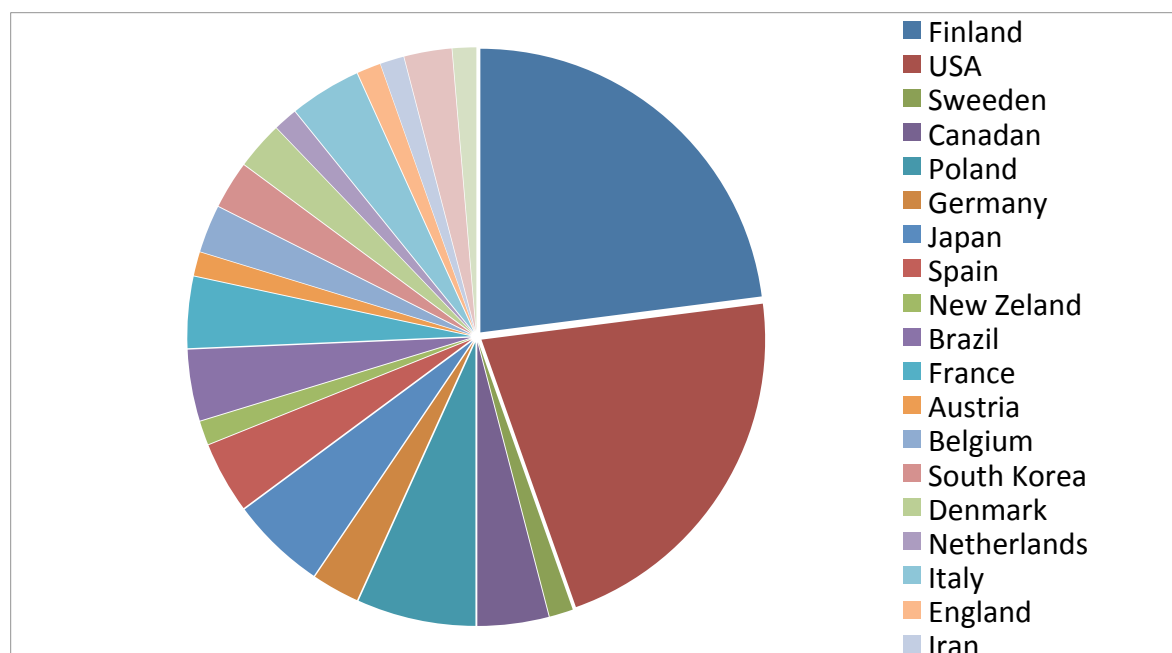


Figure 2: The location of publication of the journal articles collected and analyzed from Web of Science search terms used were (exercise*) AND (lysosome*) AND (muscle*). Location was decided by location of primary investigator.

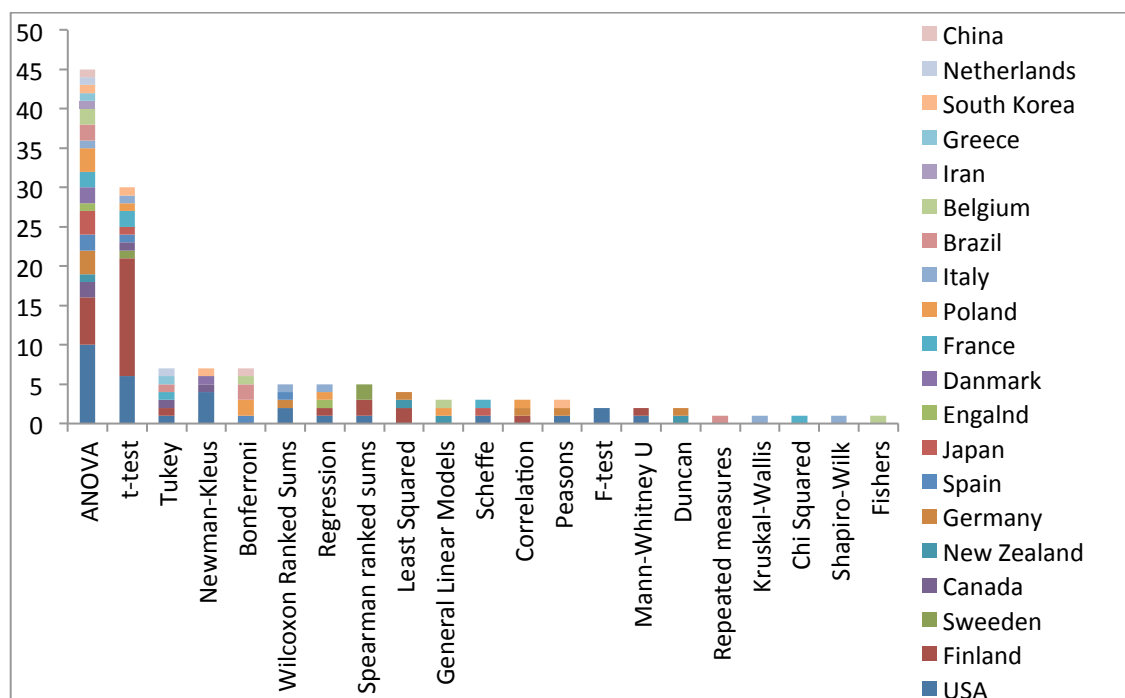


Figure 3: A Stacked bar plot indicating the statistical tests used in the studies analyzed from of the journal articles collected and analyzed from Web of Science search terms used were (exercise*) AND (lysosome*) AND (muscle*). Location was determined by location of primary investigator.

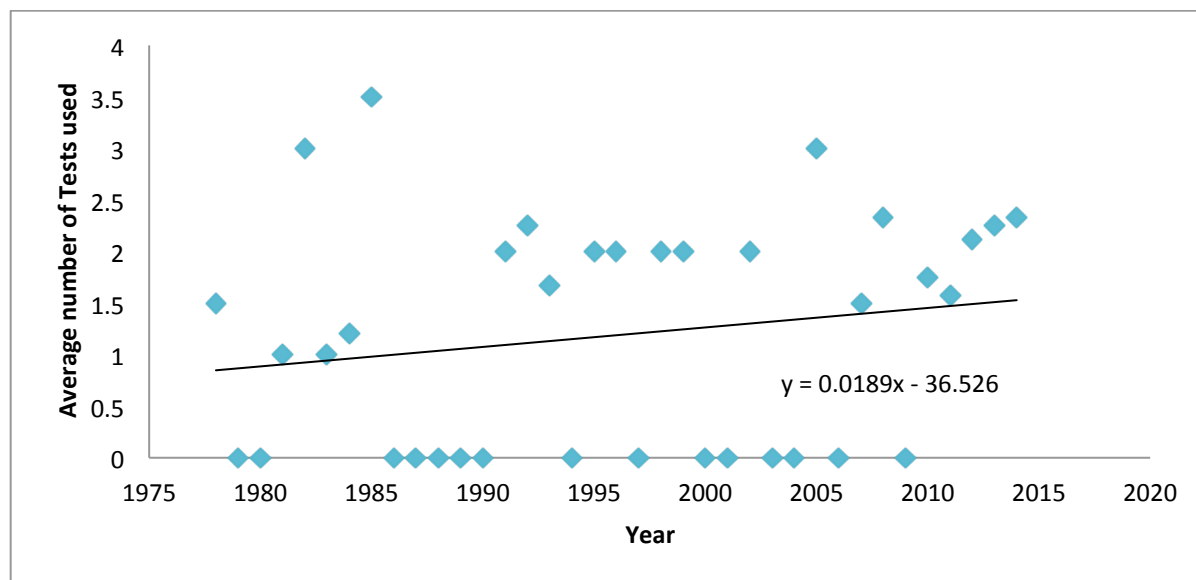


Figure 4: A scatter plot indicating the average number of statistical tests used per paper annually from of the journal articles collected and analyzed from Web of Science search terms used were (exercise*) AND (lysosome*) AND (muscle*). This was plotted against time with a line of best fit to indicate, if any, trends that exist between the numbers of tests used per year.

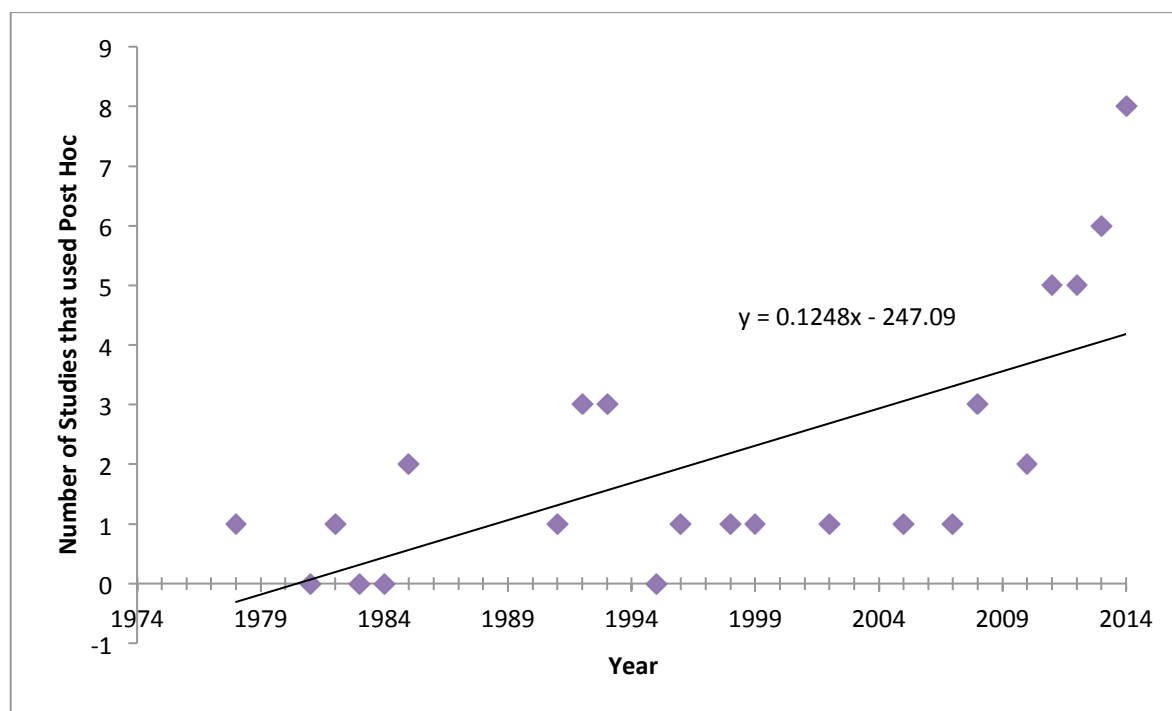


Figure 5: A scatter plot indicating the average number of post hoc tests used per paper annually from of the journal articles collected and analyzed from Web of Science search terms used were (exercise*) AND (lysosome*) AND (muscle*). This was plotted against time with a line of best fit to indicate, if any, trends that exist between the number of post hoc tests used and the year.

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