

A Systematic Review on Quiescent State Research Approaches in *S. cerevisiae*

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Abstract: Quiescence, the temporary and reversible arrest of cell growth, is a fundamental biological process. However, the lack of standardization in terms of reporting the experimental details of quiescent cells and populations can cause confusion and hinder knowledge transfer. We employ the systematic review methodology to comprehensively analyze the diversity of approaches used to study the quiescent state, focusing on all published research addressing the budding yeast *Saccharomyces cerevisiae*. We group research articles into those that consider all cells comprising the stationary-phase (SP) population as quiescent and those that recognize heterogeneity within the SP by distinguishing phenotypically distinct subpopulations. Furthermore, we investigate the chronological age of the quiescent populations under study and the methods used to induce the quiescent state, such as gradual starvation or abrupt environmental change. We also assess whether the strains used in research are prototrophic or auxotrophic. By combining the above features, we identify 48 possible experimental setups that can be used to study quiescence, which can be misleading when drawing general conclusions. We therefore summarize our review by proposing guidelines and recommendations pertaining to the information included in research articles. We believe that more rigorous reporting on the features of quiescent populations will facilitate knowledge transfer within and between disciplines, thereby stimulating valuable scientific discussion.

Keywords: dormancy; quiescence; growth arrest; budding yeast; stationary phase; G0; cell cycle; eukaryotic cell model



Citation: Opalek, M.; Tutaj, H.; Pirog, A.; Smug, B.J.; Rutkowska, J.; Wloch-Salamon, D. A Systematic Review on Quiescent State Research Approaches in *S. cerevisiae*. *Cells* **2023**, *12*, 1608. <https://doi.org/10.3390/cells12121608>

Academic Editor: Yoshikazu Ohya

Received: 3 May 2023

Revised: 2 June 2023

Accepted: 9 June 2023

Published: 12 June 2023



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1. Introduction

Quiescence is a fundamental biological state of reversible growth arrest in which cells reduce metabolic activity and halt growth, but remain capable of renewed division upon stimulation. In both single-celled and multicellular organisms, quiescence plays a crucial role in maintaining cellular integrity, tissue homeostasis, and overall organismal health [1].

In mammals, quiescence also plays a crucial role in regulating the balance between cell proliferation and differentiation [2]. For example, during neural development, neuroblast cells enter a state of developmental quiescence, which temporarily stops cell division and ensures proper differentiation. Similarly, adaptive quiescence, such as that observed in T cells, enables the immune system to maintain a pool of non-activated, yet responsive, T cells that can quickly proliferate upon encountering a specific antigen [2]. Stem cells also remain in a quiescent state until they are triggered to proliferate, either to replace damaged cells or due to an oncogenic change, which can lead to the development of cancer [1].

For unicellular microbes, quiescence is the most common state in nature and it is crucial for long-term survival under the prevailing unfavorable conditions. Indeed, proliferation may be a relatively rare event in the life history of a microbe, as the nutrients that provide the energy necessary for biomass accumulation and cell division are only temporarily

available in the environment. Although the definition of quiescence, namely that quiescence is a temporary and reversible growth-arrested state that cells can enter in response to unfavorable environmental conditions [3], captures the essence of the quiescent state, it is difficult to set the boundaries of when and under what circumstances a given cell or population of cells is quiescent.

This systematic review encompasses research conducted specifically on the budding yeast *Saccharomyces cerevisiae*, an excellent eukaryotic model organism frequently used in a variety of fields within the natural sciences [4]. Importantly, fundamental biological processes are conserved among eukaryotes, and the cellular organization of the yeast cell is similar to that observed in higher organisms, including humans [5]. Many fundamental biological processes have been described for the first time in budding yeast, including recent work on the mechanisms of apoptosis, for which the Nobel Prize was awarded in 2016 [6]. Because *S. cerevisiae* can be used for such a broad range of research, we believe that this systematic review provides a good overview of the current state of quiescence research.

Although the terms “quiescent”, “stationary phase” and “G0” are often used interchangeably [7], we suggest separating them, following the proposition formulated almost two decades ago [8]. This proposition is that the “stationary phase” is a part of the microbial culture growth curve, which indicates that a given population has used all available its resources and has reached maximum density for a given condition. It is important to stress that not all non-proliferating cells present in the stationary phase are quiescent. Senescent cells are unable to resume cell division and will die in the future. Additionally, in the stationary-phase population, there are cells of varying age, as well as the dead ones; therefore, such a population comprises cells in diverse physiological states rather than quiescent cells only. “G0” refers to a cell that has exited the cell cycle, typically from the G1 phase, and it does not indicate whether this arrest is reversible. The term “quiescent” describes cells’ ability to survive and their capacity to re-enter the cell cycle. The other form of growth arrest can be observed in diploid yeast strains that can sporulate via meiosis. Although yeast spores and quiescent cells share common characteristics, with the most important being their ability to resume growth, their underlying molecular mechanisms are different [9]; therefore, research articles studying spores are excluded from this review.

Heterogeneity within stationary-phase yeast populations was first described in 2006. The classic publication by Margaret Werner-Washburne’s group [10] described a method via which to isolate two subpopulations from the stationary phase using density centrifugation: the less dense upper fraction, called non-quiescent (NQ), and the denser lower fraction, called quiescent (Q). In the same year, Yang et al. (2006) [11] identified five phenotypes in the stationary phase based on nuclei morphology and the degree of chromatin condensation.

In a laboratory set-up, quiescence is usually triggered by gradual carbon starvation; however, cells can enter the quiescent state in response to the limitation of other key nutrients too. Importantly, depending on the limiting nutrient, the cellular response may differ [12]. There are distinct genes that are needed for a cell to survive the starvation of a particular nutrient and the resulting metabolic profiles of starved cells are also different [12]. For example, respiration and functional mitochondria are crucial for survival during glucose starvation, while vacuole and autophagic pathways are needed in nitrogen starvation [12,13]. Additionally, the ability of cells to synthesize all compounds required for growth (prototrophy) is crucial for surviving starvation [14,15]. Recently, Santos et al. (2021) [15] conducted a high-throughput analysis and concluded that due to the complex interplay between the strain genetic background (auxo/prototrophy), gene deletions, and media composition, quiescence should be studied using prototrophic strains only. Taken together, there is no one universal quiescent state, but rather a combination of environmental effects and cellular variations that lead to reversible growth arrest [16,17].

Growth arrest is associated with a variety of cellular rearrangements; however, the presence or lack of those characteristics is not enough to predict cell fate, particularly whether a given cell will or will not be able to resume growth under favorable conditions.

Importantly, entry into quiescence is a gradual process that can take days to establish and it is not common to all cells. The actin skeleton is transformed into spheroid actin bodies, the mitochondrial network is condensed into multiple vesicles, and there is an accumulation of storage materials, particularly trehalose [16–19]. Not only are organelles rearranged, but the genome is also adjusted, including global chromosome condensation and telomere clustering; meanwhile, proteins, enzymes, and mRNAs are condensed and encapsulated into stress granules and P-bodies [17,20–22]. Note, however, that not only can these characteristics vary from cell to cell (i.e., not all Q cells will share the same universal characteristic), but they can also change over time [17]. In particular, the longer a cell remains in the quiescent state, the more time it may need to re-enter the cell cycle [23]. In addition, after a long period of time, quiescent cells can accumulate damages that commit them to senescence and subsequently to apoptosis [17].

Quiescence provides protection from a variety of environmental stressors. For example, quiescent cells have been shown to be more resistant to high temperatures [18], oxidative stress [12], antibiotic treatment [24], and prolonged starvation [25].

The essence of the quiescent state, namely the ability to re-enter the cell cycle, makes the study of quiescent cells extremely challenging. This is because some assumptions and/or predictions about the fate of non-proliferating cells have to be made before such a cell can prove its ability to resume growth. Unfortunately, given the diversity of scenarios, it seems impossible to provide a more precise and rigorous definition of quiescence.

The aim of a systematic review is to provide a comprehensive and unbiased synthesis of findings in the area of interest. We use the systematic review methodology to capture and categorize the current state and diversity of all published research conducted on *S. cerevisiae* quiescent cells. This involves searching both scientific databases and classified article texts using pre-planned procedures (see Section 2 for details), which minimizes the bias and ensures that all relevant articles are taken into account. A systematic review focuses on summarizing and synthesizing research, while a meta-analysis, which may follow, goes a step further by quantitatively analyzing the effect sizes across studies. An analysis of effect sizes is not performed in this review. Following the recommendations of Foo et al. (2021) [26], we identified the objectives of the review (described below), then formulated and tested search strings. We then performed an initial screening, which is a classification of research articles based on the following: *titles*, *abstracts*, and *keywords*. Finally, we conducted a full-text screening of the selected articles (see details in the Section 2).

We classified the selected articles according to the following information: (1) what the authors mean by “quiescence”, i.e., whether the whole stationary-phase population is treated as quiescent, or some subpopulations are distinguished within the stationary-phase culture; (2) how old the studied populations/cells are; and (3) how quiescence is induced. We also noted (4) the metabolic profile of a strain, in particular whether it is prototrophic or auxotrophic, and its origin (laboratory or wild). We further recorded which (5) biological aspects are studied in the analyzed research article in order to illustrate how broad the implications of quiescence can be. Moreover, we analyzed how these features change over the years. We combined the above features and identified the most and the least frequent experimental set-ups. Finally, we propose a set of guidelines that, we believe, can improve research clarity and facilitate knowledge transfer. We also discuss several directions that the field of quiescent could pursue.

2. Methods

2.1. Literature Search

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. We searched three databases (Scopus, Web of Science and PubMed) for records published up to the end of 2022 (Figure 1A, see search strings in the Supplementary Materials). The deduplicated records were uploaded to Rayyan (<https://www.rayyan.ai/> accessed on 1 December 2021) for the initial screening based on titles, abstracts and keywords. The screening was carried

out independently by three scientists. The records were classified according to the decision tree (Supplementary Materials). Specifically, we excluded articles that were not written in English, those that did not use *S. cerevisiae*, and all publications types other than original research articles. We excluded articles in which “stationary phase” was not the subject of the research (e.g., the stationary phase was used only to refer to the age of a population). The full texts of the 402 included records were then acquired using Zotero reference manager (<https://www.zotero.org/> accessed on 1 December 2021). Three scientists performed the full-text analysis, each analyzing ~130 articles. At this stage, 205 articles were excluded, and the reasons for their exclusion are provided in the Supplementary File. Finally, 197 articles were included and analyzed within this systematic review. The database and literature search procedures are summarized in a PRISMA diagram (Figure 1A,B). The selected articles were screened for the following features: (1) meaning of quiescence, (2) age of studied populations, (3) method used to induce quiescence, (4) metabolic profile and origin of used strains, and (5) biological aspects studied within the given article (see details in Tables S1–S5). In all cases (except for metabolic profile), the categories distinguished within a feature were non-exclusive, i.e., a single research article could be classified into more than one category within a single feature.

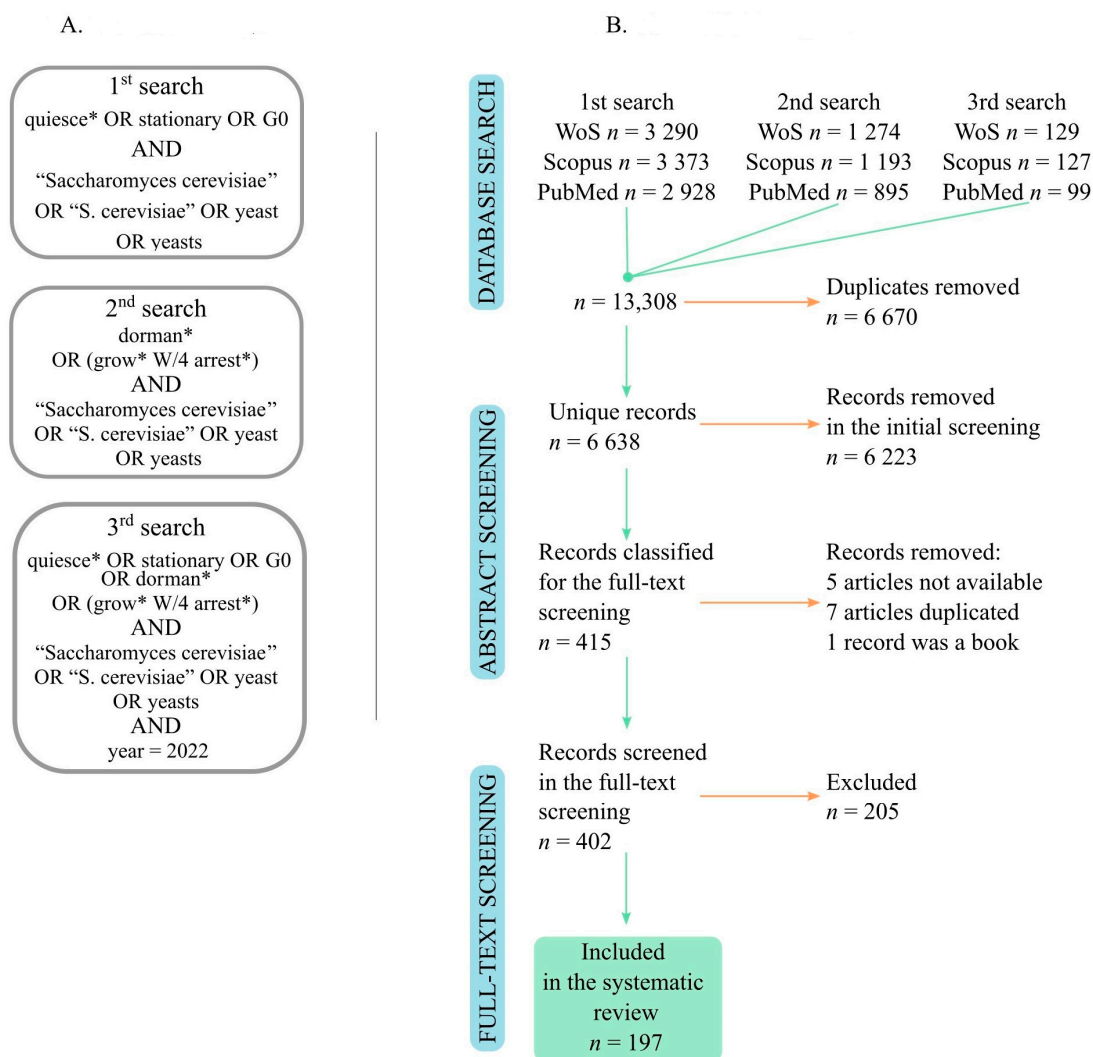


Figure 1. (A) The search strings used to find records in the databases. The asterisk (*) indicates a wildcard character for any combination of characters that could follow the prefix. See the Supplementary Materials for details. (B) The PRISMA diagram of the classification of records in this systematic review. See the Supplementary Materials for details.

3.2. The Meaning of “Quiescence”

We analyzed whether, within a given publication, the whole stationary-phase population is treated as quiescent (*whole_pop*), or whether some phenotypically distinct subpopulations are distinguished (*subpop*), (Figure 3, Table S1). Research on non-purified whole stationary-phase cultures prevails; however, in recent years, authors have more frequently considered the phenotypic variability of cells within the stationary-phase population. Among all the articles analyzed, 28% take into account the heterogeneity of SP, while from 2015, this percentage increases to 42%, and in the last 3 years (from 2020), subpopulations are distinguished in 46% of the articles. Out of the research articles that consider SP heterogeneity, 86% use the density gradient fractionation procedure proposed by the Werner-Washburne group [10].

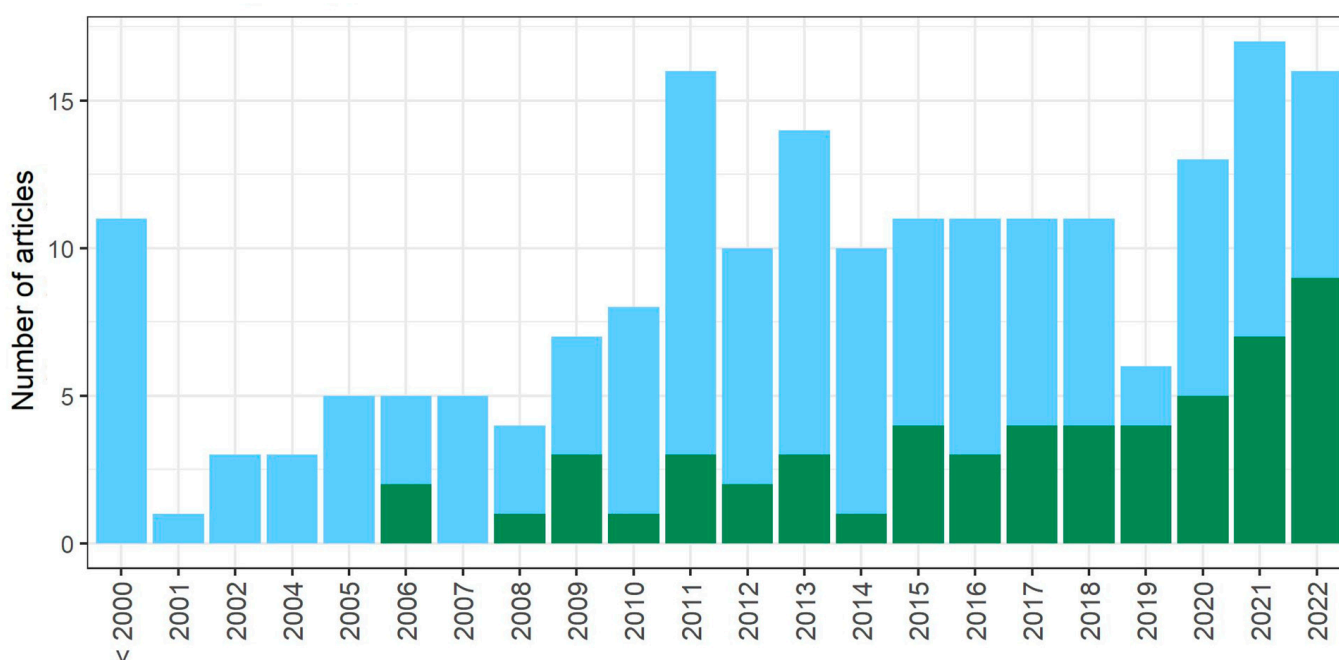


Figure 3. An overview of the approaches used to define quiescent populations over the years. Blue corresponds to articles in which the whole stationary-phase population (*whole_pop*) is treated as quiescent, while green corresponds to articles in which some subpopulations are distinguished within the stationary-phase culture (*subpop*).

3.3. The Age of Studied Quiescent Populations or Cells

Within this review, we classify the chronological age of the population into 6 categories (Table S2). The majority of research focusing on quiescence is carried out on 2–7-day-old populations (61% of articles) (Figure 4). Interestingly, in older populations (age categories more than 4 days of growth), a similar number of articles treat the whole SP population as quiescent and distinguish subpopulations in the SP. Additionally, we could not assign the age of the population in 45 articles. These include studies in which the age was not clearly specified and theoretical (modelling) studies that were based on already existing datasets.

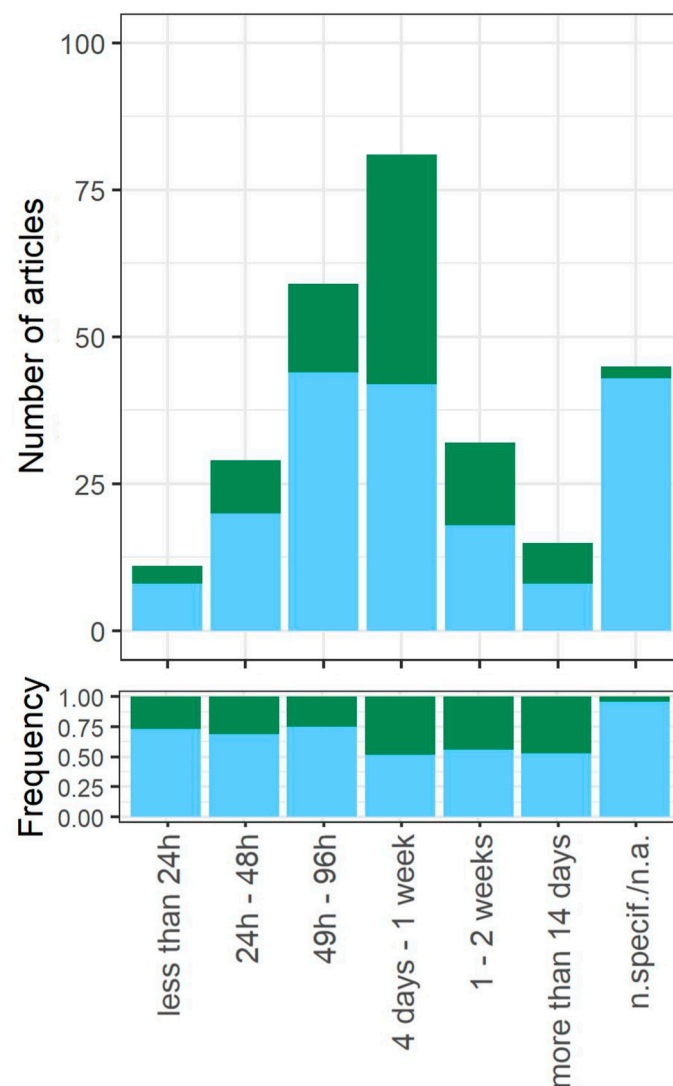


Figure 4. The distribution of the age of studied quiescent populations among the analyzed research articles, shown as an absolute number of publications and frequencies. Blue corresponds to articles in which the whole stationary-phase population (*whole_pop*) is treated as quiescent, while green corresponds to articles in which some subpopulations are distinguished within the stationary-phase culture (*subpop*).

3.4. Starvation Induction

In most research articles, to obtain quiescent cells, populations were kept in a growth medium for a certain period of time (chronological age, *gradual_starvation*, 86% of articles, Figure 5, Table S3). However, we also distinguished articles in which cells were arrested by transfer from rich to starvation medium or by the addition of growth-arresting factors (e.g., rapamycin or alpha-factor, referred to as *abrupt_starvation*, in 24% of articles). We did not recognize any pronounced patterns or interdependences between the populations' age, the method of starvation induction, and the definition of quiescence applied in a given research set-up (Figure 5).

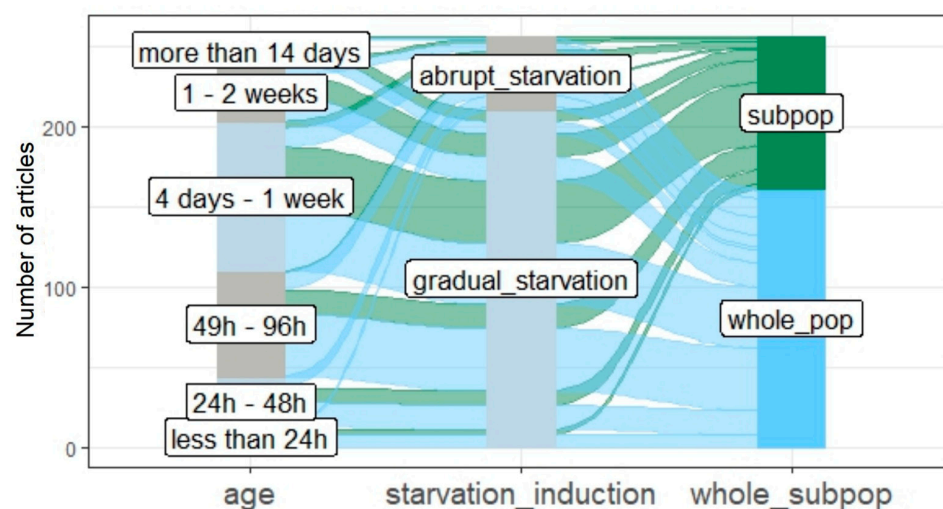


Figure 5. The visualization of dependencies between features of studied quiescent populations. The first column (*age*) corresponds to the categories within the feature *age of studied populations or cells* (Figure 4). The second column (*starv_induction*) corresponds to the method by which starvation was induced, the third column (*whole_subpop*), as well as the colors, correspond to the meaning of quiescence adopted within a given research article.

3.5. The Metabolic Profile and Origin of Studied Strains

We report whether *prototrophic* or *auxotrophic* strains were used within a given research article (Figure 6, Table S4). The majority of research has been carried out using auxotrophic strains only (63% of articles). The use of prototrophic strains was rare before the 2010s (22%) and between 2020–2023, it increased to 31% (Figure 6). Interestingly, research conducted using prototrophic strains more frequently distinguishes the subpopulations in the stationary-phase cultures ($\chi^2 = 11.97$, $df = 2$, $p = 0.0025$). We also noted whether the origin of the strain was *lab* (laboratory) or *non-lab* (including wild and industrial strains). Currently, research on quiescence seems to be limited to laboratory strains. We recognized only five research articles in which *non-laboratory* strains were studied, all of which were fermentative strains used in the production of alcoholic beverages.

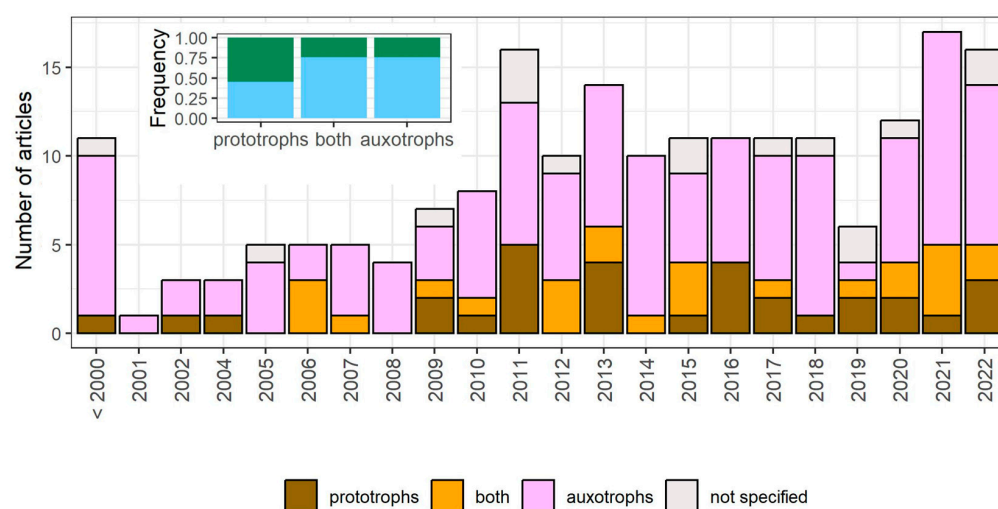


Figure 6. Usage of *prototrophic* (brown), *auxotrophic* (purple) and both prototrophic and auxotrophic (orange) strains of *S. cerevisiae* over time and the total frequency of each metabolic profile. On the frequency plot, blue corresponds to articles in which the whole stationary-phase population (*whole_pop*) is treated as quiescent, while green corresponds to articles in which some subpopulations are distinguished within the stationary-phase culture (*subpop*).

3.6. Biological Aspects

We identified 10 categories of BIOLOGICAL ASPECTS that were studied in the analyzed research articles (Figure 7). Details of all the categories can be found in the Supplementary Materials (Table S6). Note that the categories are not exclusive, i.e., several biological aspects can be studied within a single research article.

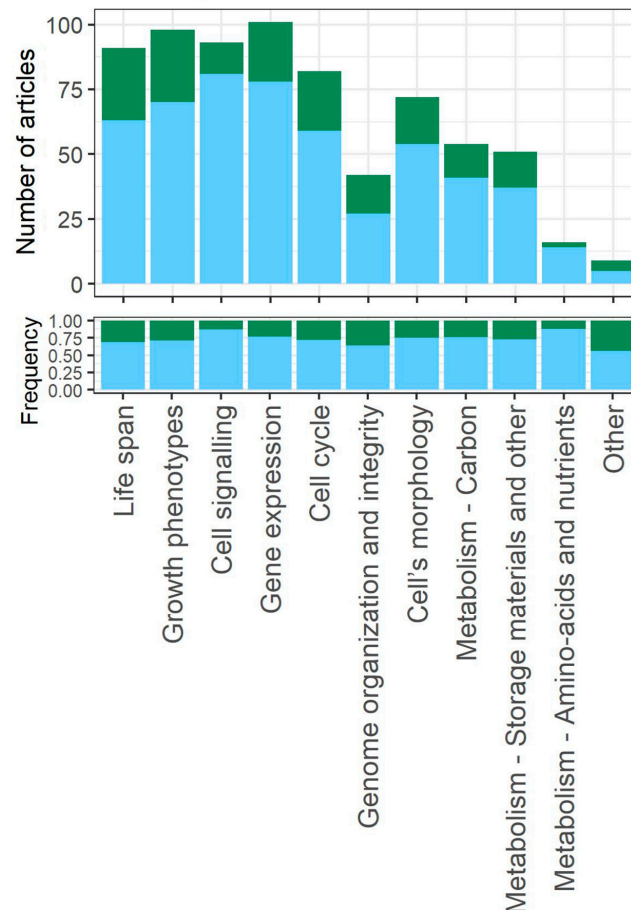


Figure 7. Number of articles and frequency of the biological aspects studied within the research articles included in this systematic review. Blue corresponds to articles in which the whole stationary-phase population (*whole_pop*) is treated as quiescent, while green corresponds to articles in which some subpopulations are distinguished within the stationary-phase culture (*subpop*).

Within all 197 research articles analyzed, the most frequently studied category was *gene expression* (100 articles), which includes RNA-based investigations as well as the mechanism and regulation of protein synthesis. The transcriptomic profiles of proliferating and quiescent cells differ significantly. Moreover, transcription in quiescent cells can be further influenced by various factors, such as environmental signals and the genetic background. Consequently, the analysis of gene expression patterns appears to be a significant aspect of numerous research articles. The *cell signalling* category (93 articles), which gathers research on various signalling pathways, was also very common. There are two ecological categories: *life span* (91 articles), which focuses on aspects related to chronological ageing, and *growth phenotypes* (98 articles), which includes research articles that have studied various population features, such as cells' survival rate or their ability to grow in response to stressors. Quiescence entry in the context of the *cell cycle* was studied in 82 articles, and *genome stability* was the least frequent aspect, studied in 41 articles. Microscopic investigations of *cell morphology* were conducted by the authors of 72 articles. Studies related to *metabolism* (altogether 83 articles) fall into three categories: those related

to *carbon metabolism* (54 articles), *amino acids and nutrients* (16 articles), and *storage materials* (51 articles).

3.7. Experimental Set-Up

Using the categorization proposed within this review, the number of possible experimental set-ups could be as high as 48 (*age* (6 categories) \times *metabolic profile* (2 categories) \times *quiescence meaning* (2 categories) \times *starvation induction* (2 categories)) (Figure 8). We identified the most frequent combination, which is an auxotrophic population gradually starved for 49–96 h (2–3 days) and analyzed as a whole population (without distinguishing subpopulations). This combination occurred in 35 research articles. Two other frequent combinations involve a auxotrophic population gradually starved for 4–7 days and analyzed as a whole population (25 articles) or with the identification of subpopulations (24 articles). The most frequent experimental set-up with prototrophic strain(s) occurred 18 times, in which populations were gradually starved for 4–7 days and analyzed with the identification of subpopulations. Eight combinations do not occur in any article.

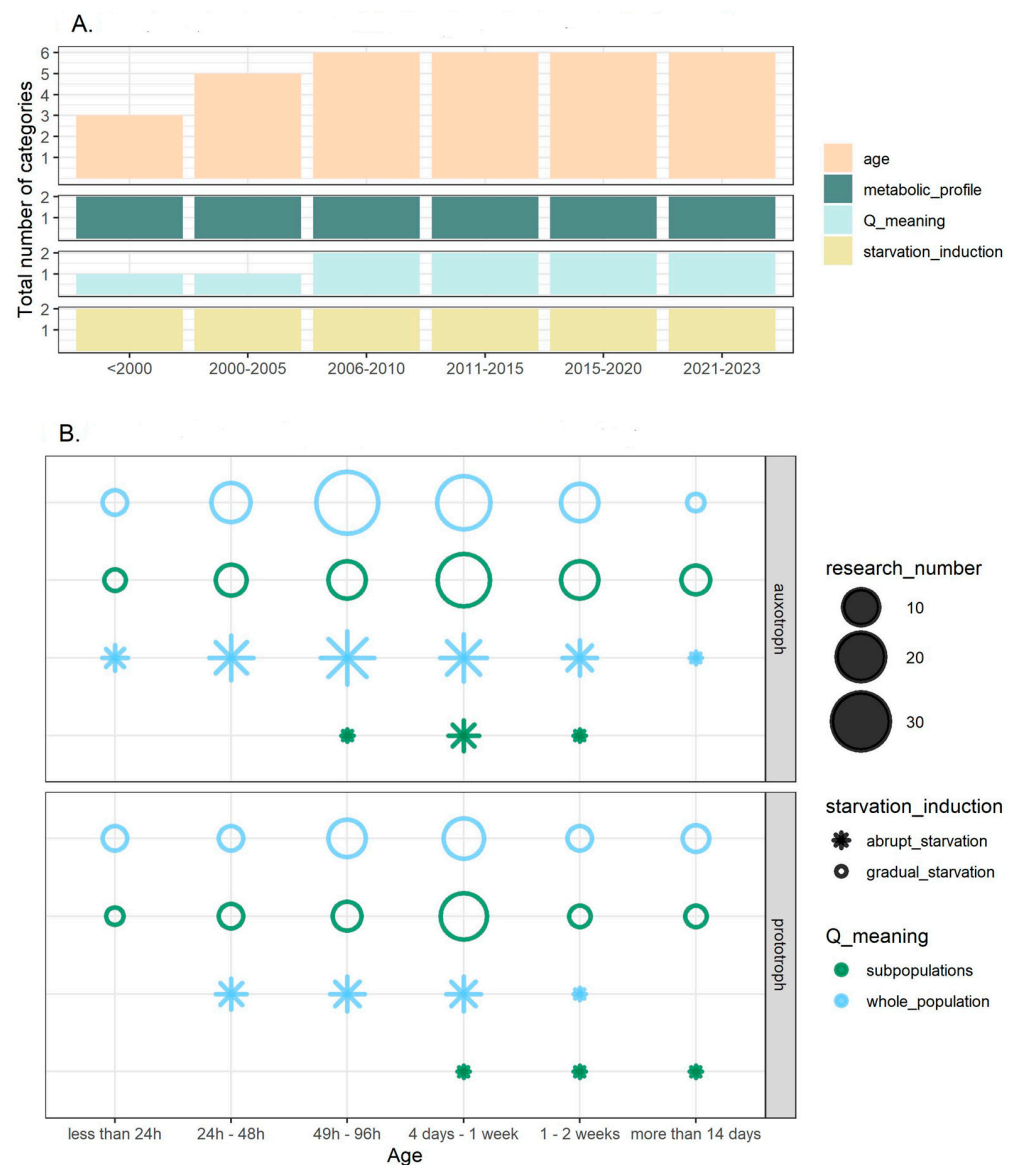


Figure 8. Visualization of experimental set-ups used to study quiescence. (A) Number of categories

frame. The maximal y-value in a given panel corresponds to the total number of categories within the feature; for example, we distinguish two categories within the feature *Q_meaning* (*whole_pop* and *subpop*) and six categories within the *age* feature (*less than 24 h*, *24 h–48 h*, *49–96 h*, *4 d–1 w*, *1–2 w*, *more than 14 d*). **(B)** Visualization of frequencies of experimental set-ups. The size of points corresponds to the number of articles within the given experimental set-up; if the point is missing, it means that no research was conducted using that experimental set-up. The shape of the point (circle/star) corresponds to the way in which quiescence was *induced* and the color corresponds to *the meaning of quiescence*. The *metabolic profile* is divided into two panels and *age* is plotted on the x-axis.

4. Discussion

This systematic review presents the diversity of research on the quiescent state in the eukaryotic cell model organism of the yeast *Saccharomyces cerevisiae*. QUIESCENCE is a broad term; therefore, to ensure the transparency and reproducibility of research across different laboratories and to facilitate knowledge transfer, it is important to define the crucial variables that vary between the research.

The major division within the research on quiescence is what the authors consider quiescence to be, namely whether the whole starved/stationary-phase population is treated as quiescent, or whether some phenotypic heterogeneity is acknowledged via the identification of distinct subpopulations within the stationary-phase population. The technique most widely used to separate quiescent (lower fraction) cells was invented in 2006 in the laboratory of Margaret Werner-Washburne [10]. The fractionation procedure is based on the assumption that growth-arrested cells tend to be denser due to the accumulation of storage materials, and as such, they can be separated via centrifugation on a density gradient. However, both the biological state and nomenclature of the subpopulations separated via the fractionation procedure are confusing. While some researchers have adopted the terms “Quiescent and Non-Quiescent”, others prefer to name them “Upper and Lower fractions” (both nomenclatures used in the original work [10]). Their argument is that all cells in the stationary-phase population that restart division when nutrients are available are Q, including some cells called NQ, and that the above method rather separates cells with a low and high amount of storage material [19]. Other identification methods use hallmarks such as histone methylation landscapes [71], the mitochondrial network morphology [19], or cytoplasmic granules [18]. However, these methods only enable the identification of heterogeneity, and not the physical separation of subpopulations and independent testing. Indeed, given the natural heterogeneity of stationary-phase populations, any attempt to physically separate subpopulations may be considered overly simplistic. We believe that this is the most striking gap in knowledge and technology. Namely, we recognize the great need to connect population-based research (mostly on Q and NQ subpopulations) with the cellular heterogeneity recognized by studies on single cells.

Although the presence of phenotypic heterogeneity in stationary-phase populations is well documented, the extent to which this heterogeneity affects population characteristics, as well as adaptations to specific conditions, is frequently unknown. For example, after experimental evolution aimed at enriching the population for quiescent or non-quiescent cells (Lower and Upper fractions, respectively), the proportion of Q (L) cells varied from 95% (Q-enriched) to 13% (NQ-enriched), whereas the ancestral strain had 75% Q cells [67]. In this case, the Q-enriched population can be roughly treated as homogeneous, while making the same assumption for the NQ-enriched population would be incorrect. On the other hand, the article by Sagot and Laporte (2019b) [17] shows heterogeneity even within quiescent cells, which are often believed to fall mostly into the Lower fraction. Altogether, the heterogeneity of the stationary-phase population needs to be taken into account in order to make further assumptions, although physical separation into multiple homogeneous subpopulations may be impossible or may additionally affect cells’ entry into quiescence and/or cellular properties.

Cell properties change with the time spent in starvation, during the so-called chronological ageing [7,17]. The transition to quiescence begins before nutrients are exhausted,

and the gradual slowing down of metabolic activity takes days to establish (see review [7] for details). Authors should therefore carefully decide upon the time point at which they determine and name the cell or population to be “quiescent”. In particular, they should decide how long the population should be kept in starvation for all cells to achieve the quiescent state and whether, for example, 2-day-old and 7-day-old quiescent cells are significantly different, taking into account the specific conditions of a given experiment. The commonly used statement declaring that “the population has been grown to stationary phase” traditionally refers to a 24 h old, overnight, population with an average density of 2×10^8 cell/mL. However, this description is not precise enough for quiescence identification. The physiological state of the cell changes with age, particularly at the onset of starvation (approximately up to 7 days), so chronological age is an important feature of the population. In 45 articles, we failed to assign the correct age to the populations being studied. This might cause major problems in the interpretation of results.

Another aspect related to nutrient limitation is the method applied in order to induce starvation/quiescence entry. We noted whether cells were allowed to adapt slowly to the decreasing amount of nutrients, or whether they were suddenly transferred to starvation media and/or a growth-arresting treatment was applied. This classification is important because gradual nutrient limitation leads to a different physiological state to that induced by an abrupt transfer to a nutrient-limited environment. In particular, nutrient transporters have varying levels of efficiency, which are adapted to the availability of a given substance in the environment. Consequently, the gradual depletion of a nutrient is reflected in progressive switches in the appropriate transporters, which is not the case when the environment is suddenly changed [7]. Although cells are adapted to gradually decreasing nutrients, both *abrupt* and *gradual* quiescence inductions can mimic naturally occurring ecological scenarios. For example, abrupt nutrient deprivation can occur when yeasts growing on ripening fruit are suddenly washed into the soil by rain. Nevertheless, the way in which quiescence entry is induced is a major signal and can influence a variety of cell properties. Therefore, we argue that the way in which starvation is induced should be thoroughly described in the article, and not just mentioned in the Section 2, especially in the case of the less frequently used methods of abrupt growth arrest.

Quiescence entry is a complicated and multi-step process that requires energy and extensive adjustments in cell functioning. Thus, any genetic disruption, especially one that affects nutrient uptake and amino acid synthesis, has a pronounced effect on cellular properties and consequently on survival [14]. Within this review, we report whether *prototrophic* or *auxotrophic* (or both) strains were used. There is evidence that auxotrophs may be short-lived and lack the characteristic of quiescence, due to disruptions in growth-controlling pathways [14,15]. Moreover, amino acid over-supplementation in order to compensate for genetic defects causes further nutritional imbalances that additionally shorten the chronological life span [7,14]. Laboratory strains with trophic markers (auxotrophs) are widely used because they are easy to select on a specific media. However, gene deletions, such as those seen in auxotrophs, have a pronounced effect on cell function and may interfere with proper quiescence entry. Furthermore, when using auxotrophic strains in research, it may be difficult to distinguish the effect being studied from the effect of disrupted amino acid synthesis. For example, it has been shown that quiescent cells are more sensitive to UV radiation [105], but as this was carried out using auxotrophic strains, it is unclear whether the same sensitivity would be seen when testing prototrophs. According to current knowledge, auxotrophs should be avoided when studying quiescence [7].

We were also interested in whether research on *S. cerevisiae* quiescence is limited to laboratory strains or whether there have been some attempts to study this phenomenon in wild/non-laboratory strains. We recognized only five research articles in which *non-laboratory* strains were used [47,58,72,87,191]. Laboratory strains are unlikely to be good representatives of microbes isolated from nature [219]. There is a growing interest in wild yeast [220], so studying quiescence in wild isolates can provide valuable insights, for example, into how universal traits are, even just within the *Saccharomyces* sp. group.

The fundamental importance of quiescence is reflected in the broad range of research fields (biological aspects) we identified (Figure 7). Quiescence can be studied at the gene-level in order to discover the mechanisms responsible for the transition, the biochemical processes that enable this cellular response, and finally how these changes affect ecological aspects, such as cells' survival and resistance to environmental changes.

Finally, we investigated the experimental setups used to study quiescence by combining the information on the populations under study. We report that since 2006, all the categories of analyzed features that we defined are present in the experimental set-ups (Figure 8A), which means that the diversity of approaches used to study quiescent state is steadily present in research. We also analyzed which experimental set-ups are the most and the least frequently used to study quiescence, which can help to identify knowledge gaps. In particular, there are eight theoretically possible experimental set-ups that have never been used to study quiescence in budding yeasts (Figure 8B).

We also noticed an interesting connection between the age of the studied population and the frequency of the subpopulations being distinguished within the SP (Figure 4). In particular, the older the population studied, the more frequently subpopulations are distinguished. Although this correlation is not statistically significant (Spearman rank correlation $r = 0.65$, $p = 0.17$), we recognize this as an interesting research area. Cells tend to be more homogeneous in younger populations; in particular, cells can synchronize during proliferation, and the diversification starts when nutrients become limiting. The heterogeneity increases with the time spent in starvation, as the fraction of cells that enter quiescence can increase, while older/damaged cells commit to senescence or apoptosis. Although in bacteria survival during the stationary phase (LTSP) and the evolution of growth advantage in stationary-phase (GASP) mutants are well studied [221,222], there are only limited reports regarding yeast [223]. Indeed, studies on the evolution of quiescence and phenotypic heterogeneity in the long-standing stationary phase are potential intriguing future research directions.

Our systematic review could be a valuable source of information for higher-level comparisons, such as a meta-analysis. The database we have compiled makes it easy to identify studies that have been conducted using a specific methodology and contain empirical results. This tool can be used to address a variety of research questions, such as the effect of metabolic profile on quiescent characteristics.

In conclusion, this review demonstrates how diverse the understanding of quiescence can be within research articles on *Saccharomyces cerevisiae*. Based on this review, we have prepared guidelines for publishing authors (Box 1). It is crucial to report the following: whether the whole population was treated as quiescent, or some subpopulations were distinguished; what the chronological age of the quiescent populations/cells studied was; how quiescence was induced (i.e., whether the population was left to starve in growth media or an abrupt environmental change occurred); and whether the strain(s) used were prototrophic or auxotrophic. These features should not only be carefully reported in the Section 2, but should also be considered when designing an experiment. We encourage the scientific community to provide more detailed justification and explanation for their research. We believe that such details will facilitate knowledge transfer and stimulate valuable scientific debate.

Box 1. Guidelines on what information should be provided by authors when studying quiescence in the budding yeast.

1. DEFINE STUDIED QUIESCENT CELLS

- Do you treat the whole stationary-phase population as a homogenous entity with only quiescent cells, or do you distinguish cell subpopulations with distinct phenotypes?
- What method do you use to separate/identify cell subpopulations/phenotypic heterogeneity? Is this method described in the literature or is it novel? If possible, describe how the used methodology relates to other methods of identifying phenotypic heterogeneity in the stationary-phase populations.

2. SPECIFY HOW QUIESCENCE IS INDUCED

AND THE TIME WHEN YOU ASSUME THE POPULATION ENTERED QUIESCENCE

- How is quiescence induced? Do you leave cultures to starve for some time (how long?) and allow cells to adjust to gradual nutrient depletion? Do you use any growth-arresting reagents? How long is a population left to grow before growth-arresting treatment is applied?
- How long does the population grow before the conduction of tests/experiments?
- What is the growth-limiting nutrient?
- Specify the growth conditions (e.g., initial cell density, inoculum size, media composition and volume, inoculum size).

3. DEFINE THE METABOLIC PROFILE AND GENETIC BACKGROUND OF USED STRAINS

- Is the strain auxotrophic or prototrophic? Specify all trophic markers, and if possible, describe how such auxotrophies influence the quiescent state.
- Specify strain name and genotype (other than trophic markers).

5. Conclusions

We used a systematic review approach to comprehensively analyze the main methodological aspects of studying quiescence in *Saccharomyces cerevisiae*. Our review shows that the understanding of quiescence in this model organism is very diverse, reflects researchers' scientific perspective, and reflects the questions asked. We have observed trends in how the perception of quiescence has evolved over time. For instance, subpopulations are increasingly being recognized, and there is a growing interest in prototrophic strains. Importantly, there are no biases in the methodological approaches that have been used in studies of the different biological aspects. On the one hand, our work highlights the lack of standardization in reporting the experimental details of quiescent cells and populations, which can be confusing and misleading when drawing general conclusions. On the other hand, the diversity of methodological approaches used in the published studies may be useful for higher-level comparisons that could be made using meta-analyses. Our catalogue of studies in each category could be very useful for this purpose.

Although we have identified the most frequent experimental set-ups, it is important to note that within the research community, there is no single dominant protocol for quiescence research. To study yeast quiescent cells that are a fraction of the stationary-phase population, we recommend using prototrophic strains, gradually starved for at least 4 days. However, we believe that given the current state of knowledge, it is impossible to provide strict recommendations regarding the best approach to studying quiescence. Therefore, we focus on highlighting the crucial features of the quiescent population under study (Box 1) and encourage researchers to consider the benefits and constraints of various approaches.

Supplementary Materials: The supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cells12121608/s1>. In the Supplementary File there are the search strings, the decision tree, and Tables S1–S5 with the details on the categorization used during full-text screening. In addition we share the excel file with all analyzed information on research articles included in this systematic review.

Author Contributions: Conceptualization: M.O., J.R., D.W.-S. and H.T.; Abstract screening: M.O., H.T. and A.P.; Full-text screening: M.O., H.T. and A.P.; Data analysis: M.O., D.W.-S., B.J.S. and J.R.; Data visualization: M.O.; Writing, original draft: M.O.; Writing, reviewing: D.W.-S., J.R., H.T., A.P. and B.J.S. All authors have read and agreed to the published version of the manuscript.

Funding: The work was funded by the National Science Centre, Poland, via an OPUS grant to D.W.-S. (grant number 2017/25/B/NZ8/01035), the programme “Excellence Initiative—Research University” at the Jagiellonian University in Kraków, Poland (grant number U1U/W18/NO/28.07) to M.O., the Priority Research Area BioS under the program “Excellence Initiative—Research University at Jagiellonian University” in Krakow (grant number U1U/P03/NO/03.32) to B.J.S., the Faculty of Biology of the Jagiellonian University research subsidies (grant number N18/DBS/000019 to M.O. and D.W.-S.), the Polish National Agency of Academic Exchange (grant number PPN/PPO/2018/00021/U/00001) to B.J.S. and the EMBO Installation Grant (B.J.S.). The open-access publication of this article was funded by the programme “Excellence Initiative—Research University” at the Faculty of Biology of the Jagiellonian University in Krakow.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in the Supplementary Materials.

Acknowledgments: We would like to thank Ryszard Korona for insightful comments during the conceptualization and analysis processes and Damien Laporte for reviewing the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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