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La Medicina del Lavoro

Editorial

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The Linear Non-threshold Extrapolation of Dose-Response Curves Is a Challenge for Managing the Risk Associated with Occupational Exposure to Carcinogenic Agents

Since its definition by the US National Research Council (1983) just 40 years ago, human risk assessment is the result of a process consisting of 4 steps, i.e., (i) hazard identification, (ii) dose-response assessment, (iii) exposure assessment, and, finally, (iv) risk characterization [1]. Hazard and risk are not synonyms, though the oldest volumes of the IARC Monographs on the evaluation of carcinogenic risks to humans [e.g., 2] start with a 'note to the reader' specifying that "the term 'carcinogenic risk' in the IARC Monographs series is taken to mean the probability that exposure to an agent will lead to cancer in humans". However, the title of recent monographs has been modified to recognize that *Hazard* refers to the strength of the evidence that an agent is a carcinogen, whereas *risk* refers to the probability that a given exposure to a carcinogen will result in cancer [3] thus limiting their relevance to the first step of risk assessment. The difference is even sharper with the inclusion of mechanistic evidence, particularly from biomarkers of effect in exposed humans, as a basis to classify agents as carcinogenic to humans (group 1) or probably carcinogenic to humans (group 2A) [3]. Including such widespread mechanisms as inflammation and oxidative stress among the key characteristics of human carcinogens is undoubtedly valuable for better understanding the mode of action. Understanding the potential of a given agent to induce changes relevant to a carcinogenetic process does not help to calculate the likelihood of its occurrence.

Regulatory agencies use quantal monotonic dose-response relationships to assess risks, including occupational ones. The dose-response relationship is usually sigmoidal or Italic S-shaped: small doses do not appear toxic up to a particular point of departure (threshold), which can be identified as a NOAEL (No Observed Adverse Effect Level), i.e., the highest dose at which no detectable adverse effects occur in an exposed population, including its most susceptible fraction. From the NOAEL, Occupational Exposure Limits (OELs) are derived as environmental concentrations not to be exceeded in managing the risk of adverse health effects at the workplace [4]. Such a deterministic approach is also applied to carcinogenic substances acting as promoters or epigenetic modulators, thereby increasing the carcinogenic risk with mechanisms other than a direct effect (damage) on DNA sequences coding for oncogenes.

It is generally considered that genotoxic carcinogens do not have a threshold, i.e., that no dose is safe. The dose-response relationship at low exposure levels is obtained by extrapolation from the LOAEL (Lowest Observable Adverse Effect Level). The LOAEL can be either a high dose of a carcinogen administered to experimental animals showing a significant increase in cancer incidence or the airborne concentrations occurring in occupational settings where epidemiological studies showed an excess of cancer incidence. From the LOAEL onwards, the dose-response curve fits experimental or empirical data. In contrast, the censored segment, for which data are missing, is extrapolated back to the origin (i.e., to zero for both dose and response), thus adopting the linear non-threshold (LNT) model [5]. Other models could be used, e.g., the one-hit, the multi-stage, and the multi-hit, but the risk estimate per unit of dose would differ by orders of magnitude from each other [1]. On the other hand, biological responses may be proportional to the logarithm of the dose, but there is no way to put negative values or zero on a logarithmic axis.

In his historical account published in this journal issue [6], Calabrese reports the fundamental role of two scientists, Gofman and Tamplin, in adopting the LNT assessment of cancer risk due to ionizing radiation exposure. He also highlights the controversial and non-evidence-based aspects in this context, as he had already reported in previous papers [e.g., 7]. Acknowledging the weaknesses of the LNT foundations calls for a desirable debate on the extrapolation to zero of the dose-response curves for ionizing radiations, recognizing that they are biased. LNT extension to carcinogenic chemicals, particularly those with radiomimetic properties, should also be revised, considering new subsequent scientific acquisitions such as DNA repair enzymes or epigenetic mechanisms acting with deterministic, and hence threshold mode of action.

Risk assessment is evolving into new approach methodologies aimed to reduce or replace animal testing by using *in silico, in vitro*, omics, cellular, micro-arrays, and more complex system data to be analyzed in the framework of mechanism-based risk assessment. In addition to incorporating physiological, toxicokinetic, and toxicodynamic parameters in such models, other conceptual issues must be addressed to achieve a realistic risk assessment and to set exposure limits instrumental to implementing effective prevention strategies. Indeed, applying uncertainty and safety factors when deriving exposure limits from such models may imply challenging situations in risk management [8]. Such challenging situations are already apparent for the possible effects of low doses of ionizing radiation, as the so-called natural background in some areas of our planet often reaches values higher than either the limits set or the levels measured by personal dosimetry in occupationally exposed groups, e.g., in healthcare workers involved in diagnosis and treatment activities in hospitals. Setting a limit lower than naturally occurring airborne concentrations is nonsense because measuring doses inferior to the natural background is simply impossible.

For carcinogenic elements and chemicals polluting the general environment, setting limits of exposure lower than the limit of quantification (LOQ) of techniques used for exposure assessment is also not applicable. Indeed, it would preclude exposure assessment, a fundamental step in risk characterization and management. Furthermore, a residual chance of getting cancer is conceivable even at zero exposure, as it would not avoid either spontaneous mutations or those occurring for other causes. Nor would it prevent failures to repair DNA damage. Therefore, for prevention purposes, it is more realistic either to propose a value graduation corresponding to normative guide values or to adopt the margin of exposure (MOE) strategy used for carcinogenic food constituents and contaminants, many of which are naturally occurring but at concentrations lower by several orders of magnitude than those necessary to cause cancer [8].

If the LNT extrapolation for ionizing radiations is affected by the severe limitations suggested by Calabrese's reconstruction, its extension to chemical carcinogens is also questionable. The quantal dose-response relationship is the one that characterizes the distribution of responses of individuals in a population of organisms [9]. The dose-response relationships can, in turn, be either monotonic (i.e., threshold or linear) or non-monotonic, where multiple points of inflection exist along the curve, determining U, U-inverted, and J shapes as occurs for essential nutrients or for hormesis in which we observe stimulatory effects at low doses and adverse effects at high doses, as described for radiation and many chemical agents [10, 11].

The correct definition of LNT is also crucial for another critical issue in predicting and preventing carcinogenic effects: the difference between carcinogens with demonstrable threshold and for which an exposure limit value is conceivable and chemicals without threshold. For the latter kind of chemical, it is impossible to set a limit such as that considered above. However, correctly answering the wrong question would not help prevent cancer. The right question is neither about hazard nor about exposure but rather about the risk entailed by any exposure, including zero exposure: does zero exposure mean zero risk? For agents with a demonstrable threshold, yes, whereas for genotoxic carcinogens acting by inducing mutations of critical genes, zero risk is unlikely to exist because mutations of critical genes can also occur spontaneously. Therefore, a risk as low as practically possible and measurable is the only realistic and achievable goal.

For chemicals with a deterministic mode of action and a threshold, the risk assessment should be based on the NOAEL to define exposures with no appreciable effects (e.g., the acceptable daily intake – ADI). For chemicals without a threshold, the type of risk assessment must be quantitative, i.e., based on dose-response modeling to calculate "the risk associated with a known exposure." LNT is but one risk quantification. Alternatively, the need for intervention should result from the margin of exposure (MOE) between the dose known to cause cancer in experimental studies and the actual human exposure from different sources. European Food Safety Authority (EFSA) concluded that a MOE of 10,000, based on a BMDL for a 10% extra risk ($BMDL_{10}$) in a rodent carcinogenicity study, 'would be of low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions [12].

Another aspect to be considered in risk management is the weight of evidence (WoE), i.e., the extent to which evidence supports possible answers to a scientific question. When reached, it may be expressed qualitatively or quantitatively. However, almost all cancers exhibit a baseline (background) incidence, even without specific agents. A background incidence implies that the population threshold – if one exists – has already been exceeded, and a positive dose-response gradient applies. Adding a small dose of the agent under study, with known and unknown agents causing the background incidence, will increase the lung cancer incidence proportionately to the added dose. Two assumptions are then possible: either it can be excluded that the agent under study and the background agents share some mechanistic components, and linearity is not assured, or it cannot be excluded, and linearity follows [14]. Beyond the issue of linearity, we can agree with Saracci that assumptions cannot be avoided, owing to the ubiquity, complexity, and potential impact of exposure to carcinogenic agents.

Calabrese's historical account of LNT adoption by regulatory agencies challenges a dogmatic approach to risk assessment for carcinogenic agents, demonstrating that the track has been disseminated by misconduct episodes and behaviors that lead to questioning the evidence on which the LNT has become a default "scientific" approach for genome-targeting agents. Lack of evidence does not necessarily disprove LNT. Still, it is a significant limitation of the WoE, and it calls for studies on the effects of carcinogens at low doses, contrasting with the extrapolations of expected effects from high and unrealistic doses to predict responses dogmatically.

Such studies include: (i) the systematic review of literature and assessment protocols, (ii) the appraisal and integration of the data, (iii) the assessment of biological relevance, (iv) the uncertainty assessment and communication, (v) the use of data from new approach methodologies (NAM). Furthermore, the growing knowledge of carcinogenesis's molecular mechanisms makes it possible to apply biomonitoring techniques to assess exposure and early effects. Independently of the mechanism of action of carcinogenic agents, the most reasonable approach to risk assessment and management of occupational carcinogenic risk is to ensure a safe MOE for the general population and biomarkers of exposure and effect not exceeding the reference values among potentially exposed workers.

Antonio Mutti

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Original article

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Psychometric Evaluation of GHQ-12 as a Screening Tool for Psychological Impairment of Healthcare Workers Facing COVID-19 Pandemic

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Keywords: General Health Questionnaires (GHQ-12); Occupational stress; Health-Care Workers; Item Response Theory

Abstract

Background: *The General Health Questionnaire (GHQ) is a widely used tool in clinical and research settings due to its brevity and easy administration. Researchers often adopt a dichotomous measurement method, considering a total score above or below a certain threshold, leading to an extreme simplification of the gathered data and, therefore, the loss of clinical details. In a multistep evaluation study aimed at assessing health care workers' mental health during the COVID-19 pandemic, GHQ-12 proved to be the most effective tool to detect psychological distress compared to other scales. These results deepened the understanding of GHQ-12 properties through a statistical study focusing on items' properties and characteristics.* **Methods:** *GHQ-12 responses were analyzed using Item Response Theory (IRT), a suitable method for scale assessment. Instead of considering the single overall score, in which each item accounts equally, it focuses on individual items' characteristics. Moreover, IRT models were applied combined with the latent class (LC) analysis, aiming to determine subgroups of individuals according to their level of psychological distress.* **Results:** *GHQ-12 was administered to 990 healthcare workers, and responses were scored using the binary method (0-0-1-1). We applied the two-parameter logistic (2-PL) model, finding that the items showed different ways of responses and features. The latent class analysis classified subjects into three sub-groups according to their responses to GHQ-12 only: 47% of individuals with general well-being, 38% expressing signs of discomfort without severity, and 15% of subjects with a high level of impairment. This result almost reproduces the subjects' classification obtained after administering the six questionnaires of the study protocol.* **Conclusions:** *Accurate statistical techniques and a deep understanding of the latent factors underlying the GHQ-12 resulted in more effective usage of such a psychometric questionnaire – i.e., a more refined gathering of data and significant time and resource efficiency. We underlined the need to maximize the extraction of data from questionnaires and the necessity of them being less lengthy and repetitive.*

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1. Introduction

The General Health Questionnaire (GHQ) aims to provide information about an individual's mental well-being by identifying distressing symptoms [1]. Its shorter version (GHQ 12-item) has become one of the most widely used scales for assessing psychological distress and short-term changes in mental health, and its popularity can be mainly attributable to its brevity and easy administration [2].

GHQ-12 has shown strong psychometric properties and it is recommended as screening tool to detect common mental disorders as depressive, anxiety and somatic disorders [3, 4].

Several analyses explored its characteristics, especially the factor structure, mostly identifying a two-factor solution through Confirmatory Factor Analysis (CFA) techniques. The two factors commonly proposed were the Depression/Anxiety construct (related to the emotional component of psychological distress) and the Social Dysfunction construct (related to the social functioning component of the individual experiencing the distress) [5]. Other authors proposed a three-dimensional solution, comprising anxiety (4-item), social dysfunction (6-item), and loss of confidence (2-item) dimensions [6].

The use of GHQ-12 to measure the mental health status in healthcare populations is frequent, and several recent contributions gave examples of its application in analyzing psychological well-being during the pandemic [7-14]. In all these cases, the screening of the psychological status through GHQ-12 was determined according to its total score. The scores typically used are the binary scale (0-0-1-1) and the 4-point Likert-type scale (0-1-2-3). Responses to all items are summed up to a total score ranging from 0 to 12 (binary scale) or 0 to 36 (Likert scale), with higher scores indicating more severe impairment. A score above a specific cut-off (3/4 for bimodal and 13/14 for the Likert scale) indicates psychological distress and suggests further investigation for potential mental disorders [15].

A possible difference in items contribution can be lost through such a measurement method, in which each item counts the same. Indeed, every single item may have a different weight, expressing different severity of the psychological impairment measured by the test.

We proposed to analyze GHQ-12 data through Item Response Theory (IRT)-based methods as they provide more details about individual items. IRT is a specific statistical model for evaluating questionnaires, and it is a more suitable tool than the usual methodologies based on Classical Test Theory (CTT), whose use is still prevalent in the psychometric field. The strength of such a technique lies in its focus on items rather than individual scores, while in the CTT, the evaluation of test properties and item characteristics is not included.

From a statistical point of view, if the results of a test are reported as a single score, it is implicitly assumed that all the items are measuring the same trait equally therefore losing the complexity of underlying traits in psychological testing. IRT allows to evaluate individual-level distress and to describe the performances of the items on the questionnaire simultaneously may providing a better clinical insight on symptoms detected and associations with potential underlying mental disorders.

To our knowledge, few authors proposed analyzing the GHQ-12 scale via an IRT approach. In some cases, IRT was applied as a suitable tool to determine the factor structure of the scale [16, 17], and more recently through the multidimensional version of IRT [18]. For instance, the IRT approach used by Smith et al. [16] explored the fact that item phrasing, item variance and levels of respondents' distress affect the factor structure observed for the GHQ-12 and may perhaps explain why different factor structures of the instrument have been found in different populations. Other uses of IRT on GHQ-12 regard computerized adaptive testing [19] or Mokken analysis [20].

However, no studies have studied the performance of GHQ-12 with IRT in an occupational setting during a pandemic. Therefore, this work aims to perform an IRT-based analysis on GHQ-12, investigating the methodological and clinical benefits of such an approach.

2. Methods

2.1 Population Study

We conducted a multistep epidemiological study within occupational health surveillance to systematically assess healthcare workers' mental well-being during the COVID-19 pandemic in a large Hospital in Milan (Italy).

GHQ-12 was administered, jointly with the Impact of Event Scale (IES-R; post-traumatic distress, [21]) and General Anxiety Disorder Scale (GAD-7; anxiety, [22]) questionnaires, to assess the psychological impact of the pandemic and to identify possible signs of impairment, further investigated through psycho-diagnostic questionnaires and specialist evaluation.

The steps of such assessment were fully presented in a previous study [23]: for each worker, the psychological well-being was screened in three steps. The first-level questionnaire collected several personal information and data from three tests (i.e., GHQ-12, IES-R, and GAD-7). Workers who scored above the cut-off in at least one scale were further investigated by the second-level questionnaire composed of psycho-diagnostic scales to assess depressive symptoms (Patient Health Questionnaire-9; [24]), dissociative symptoms (Dissociative Experiences Scale –II; [25]) and other psychological symptoms (Symptoms Checklist-90 [26]). If the second level showed psychological impairments, an individual specialized treatment with a psychiatrist and psychologist (third-level) was offered.

In this framework, GHQ-12 (binary version) proved to be an effective screening tool, deserving a deeper investigation [27].

The occupational medicine unit, where workers underwent the periodical health surveillance already prescribed by the current Italian legislation, proposed the study protocol to all workers since July 2020. By July 2021, 990 subjects out of a total population of 1,610 had been enrolled in the study. The participation rate was 62%. In detail, 220 (13%) workers did not answer our calls or were unavailable and 400 (25%) refused to participate.

Participants were predominantly female (70%) with a mean age of 45 years (sd=11); nurses (42.5%) was the most prominent job category, followed by physicians (23.5%), administrative staff (12%), health assistants (6.5%) and other roles (16%). Four hundred and forty-six (45%) participants had the experience of working in a COVID-19 area: 25% were working with COVID-19 patients during data collection, and 20% had worked in a COVID-19 department before enrollment.

Six hundred and twenty-seven workers (63%) did not show signs of psychological impairment; 363 (37%) presented signs of psychological impairment at the first screening level (i.e., with scores above the cut-off in at least one scale among GHQ-12, IES-, R and GAD-7) and underwent the second level assessment. Among these, 231 (67%; 23% of the total sample) scored above the cut-off in at least one scale among PHQ-9, DES, and SCL-90. As a result, we were able to classify participants into three sub-groups, according to their scorings: a group with no evidence of psychological distress after first-level screening (Group 1, N=627), workers who expressed distress without severe symptoms (Group 2, N=132), and subjects who expressed signs of impairment and received psychological and/or psychiatric support (Group 3, N=231).

Out of the 363 subjects who showed psychological impairment at first-level screening, almost all (91%) scored above the cut-off (equal to 4) of GHQ-12, while about half of them over-passed the cut-off of IES-R and GAD-7 scales (53% and 56% respectively). This result suggested that GHQ-12 could determine the transition to the second level more effectively than the other scales.

Results obtained from the analysis of risk factors for psychological impairment were presented in detail in a previous paper [27].

2.2 Item Response Theory (IRT)

The basic assumption of IRT models is that a person's interactions with test items can be represented according to probabilistic relations, containing a single parameter to describe the individual's characteristics θ. The power of IRT is that it estimates item characteristics through some item parameters, which permit the calculation of the expected score at the item level (e.g., probability of 1 or correct answer if responses are binary or dichotomous) and at the test level. In addition, the person's latent trait θ_i for an individual *i* is also estimated, considering specific item characteristics and how the person answers to each item.

We applied the so-called two parameters logistic (2-PL), suitable for binary data, which uses two parameters to describe each item j, corresponding to its "difficulty" and its "discrimination". The item difficulty represents the level of latent trait for which one has a 50% probability of responding 'correctly' (or 1) to that item. In other words, if $\theta_i=\beta_j$, then $P(Y_{ij}=1)=0.5$. If $\theta_i>\beta_j$, then $P(Y_{ij}=1)>0.5$ and if $\theta_i<\beta_j$, then $P(Y_{ij}=1)<0.5$. The discriminating parameter for item j, λ_j, estimates the capacity of the item to distinguish between subjects with different latent trait levels.

Two plots are typically employed in the IRT framework to visualize the analysis results. Item Characteristic Curves (ICCs) show the probability of answering 1 to an item at varying levels of the latent trait, specifying how well an item discriminates between respondents at various levels of the latent trait. The "easier" items functions are on the left side of the plot, in the lower regions of the latent trait scale, while the more "difficult" items are on the right (in our case, they are the items that underlie more severe impairment in mental health). The discrimination parameter represents the slope, which refers to how well the item response options discriminate (or differentiate) between subjects with high and low latent trait levels.

IICs show how well and precisely each item measures the latent trait at various attribute levels. Item Information measures the strength of the relationship between an item and the latent trait. Some items may provide more information at low levels of the attribute, while others may provide more information at higher levels of the attribute.

We applied the IRT model in one of its discrete versions, based on the so-called Latent Class (LC) analysis [28, 29], whose assumption is that the population under study is composed of homogeneous classes of individuals who have very similar unobservable characteristics [30, 31]. Data were collected through a computerized database generated by REDCap [32], which was subsequently analyzed by R software [33].

3. Results

Based on the dichotomous scored version of GHQ-12, we calculated Cronbach's α equal to 0.87, indicating good internal consistency. The mean score was 3.31 (SD=3.45), with 37% of subjects scoring above the cut-off equal to 4 (indicating a general level of psychological distress). Table 1 presents the twelve questionnaire items with the distribution of the respective answers.

Item parameters estimation (difficulty and discrimination) of the 2-PL model are reported and graphically represented in Figure 1, which shows the ICCs.

Item 5 (followed by Item 7) has the lowest threshold parameter, while Item 3 ("feeling useless") and Item 11 ("thinking of yourself as a worthless person") are the most 'difficult' ones. Item 5 has a location (or difficulty) parameter equal to 0, meaning that a person with a latent trait θ at level 0 has the same probability of answering 0 or 1 to Item 5. On the contrary, a level of latent trait θ equal to 1.73 is needed for having an equal probability of answering less than/same as usual or more/much more than usual to Item 11. Concerning the discrimination parameter, Item 12 (feeling reasonably happy, all things considered) has the highest value, much greater than the others. On the other hand, Item 3 has the lowest discrimination parameter. The item provides sample information about differences across individuals when discrimination is high. Item 5 and Item 7 have the leftmost lines represented in the plot, while the curve of Item 3, which is also the less steep, is plotted on the right. The curve of Item 12 is indeed the steepest one. In the IICs plot in Figure 2, the curve of Item 12 gives much information around a value

Table 1. GHQ-12 answers distribution.

	0	1
Item 1 - Able to concentrate	75%	25%
Item 2 - Loss of sleep over worry	64%	36%
Item 3 - Playing a useful part	86%	14%
Item 4 - Capable of making decisions	85%	15%
Item 5 - Felt constantly under strain	49%	51%
Item 6 - Could not overcome difficulties	78%	22%
Item 7 - Able to enjoy day-to-day activities	55%	45%
Item 8 - Able to face problems	79%	21%
Item 9 - Feeling unhappy and depressed	68%	32%
Item 10 - Losing confidence	83%	17%
Item 11 - Thinking of self as worthless	92%	8%
Item 12 - Feeling reasonably happy	73%	27%

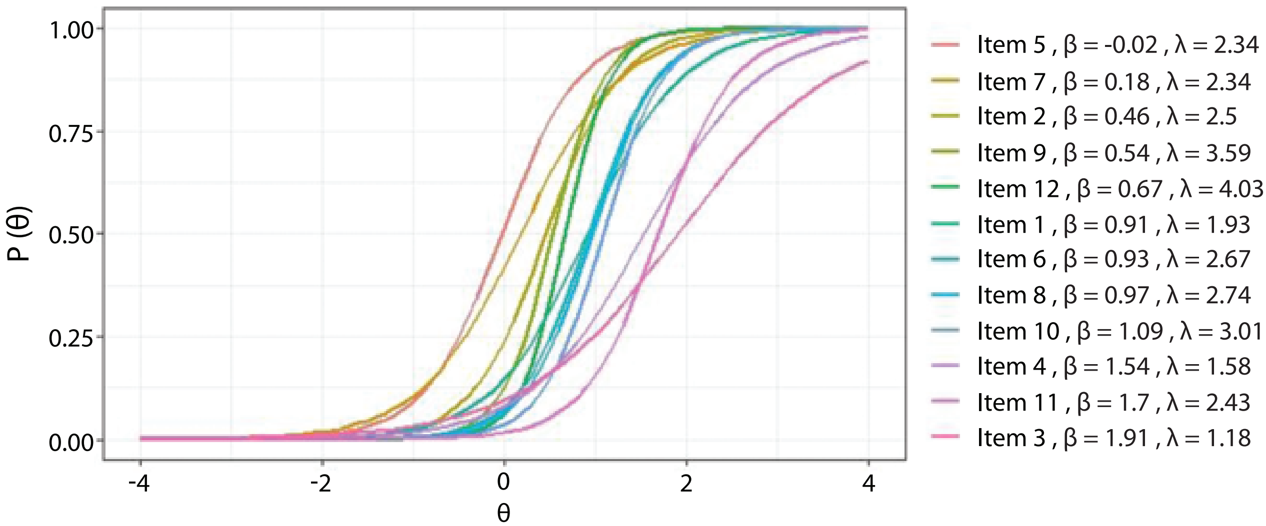

Figure 1. Item Characteristic Curves for GHQ-12 questionnaire.

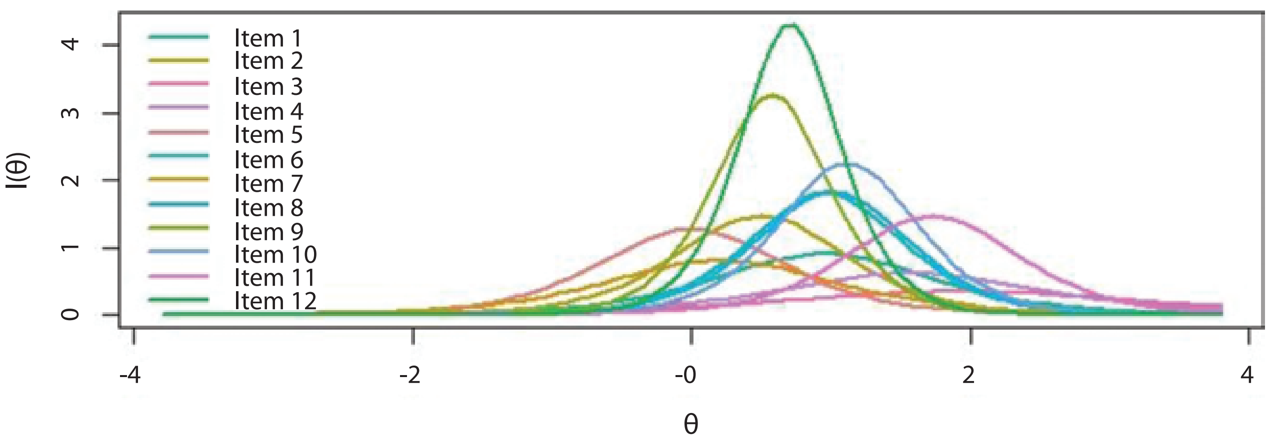

Figure 2. Item Information Curves for GHQ-12 questionnaire.

of θ between 0 and 1, while Item 3 (with the lowest discrimination parameter) gives more or less the same (low) information over a broader range.

The latent class model reaches the best fit (calculated through BIC) with three latent classes. The weights and levels of the latent trait for each dimension and latent class are in Table 2. The latent model estimates three values for the θ finding support points equal to -3.3 (low level of distress) with weight equal to 0.47, a medium level (around 0) for 38% of subjects, and a higher level of distress (θ=1.15) with weight 0.15.

We compared the three latent classes with the three groups resulting from questionnaire scorings (Group 1, Group 2, Group 3) in Table 2. Almost all (97%) subjects belonging to Class 1 did not undergo the second-level screening, i.e., they did not express any sign of discomfort through GHQ-12, IES-R, and GAD-7. On the contrary, most (85%) of those assigned to Class 3 needed psychological support, while only one-third of Class 2 required psychological therapy.

Table 3 shows the percentage of answers equal to 1 for each item, according to the latent class.

Table 2. Latent class model results and percentage of subjects by multistep evaluation.

	θ	%	Group 1 (no distress)	Group 2 (psychological distress)	Group 3 (psychological impairment)
Class 1	-3.3	47%	97%	1%	2%
Class 2	-0.8	38%	44%	20%	36%
Class 3	1.2	15%	1%	14%	85%

Table 3. Probability of answering equally to 1 by class.

	ITEM											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Class 1	3%	4%	4%	2%	17%	1%	16%	1%	1%	-	-	-
Class 2	31%	52%	17%	17%	76%	24%	64%	21%	45%	15%	6%	33%
Class 3	76%	92%	38%	50%	96%	81%	90%	81%	95%	76%	41%	97%

Participants assigned to Class 1 answered 0 for almost all the items, with the highest percentages of the answer 1 occurring for Items 5 and 7 (but much less than in the general distribution). On the contrary, considering such items (Items 5 and 7), almost everyone who belongs to Class 3 answered 0. In addition, for the group with more severe signs of psychological distress, percentages of answer 1 were much higher (than the general distribution) up to the items found to be the most "difficult" (Item 3 and Item 11). For the second class, the distribution was more balanced, and more than half of the participants answered 1 only to Item 2, Item 5, and Item 7.

4. Discussion

The GHQ-12 is frequently used among different settings and populations, and its assessment methods adopt predominantly a dichotomous scoring, which may contribute to lose potential differences in items contribution; this rationale motivated us to a psychometric analysis to better clarify the methodological and clinical quality of this tool. The analysis was carried out within a study aimed to evaluate psychological well-being of healthcare workers in a large Hospital in Milan (Italy) facing COVID-19 pandemic.

In our scenario, the IRT was a suitable tool for scale assessment. Instead of considering the single overall score, in which each item accounts equally, the item-based analysis produced interesting results by identifying specific items able to detect psychological impairment effectively.

Such considerations are similar to those obtained in previous analyses on GHQ-12 based on IRT methods in other frameworks. For example, the approach of Smith and colleagues [18], within the multi-dimensionality assessment of GHQ-12, showed how the use of the summated scores for the GHQ-12 could potentially lead to an incorrect assessment of patients' psychiatric morbidity.

The focus on items characteristics allowed us to deeply investigate how the mental health status was captured by GHQ-12 in our population, identifying different levels of severity (given by item difficulty) and quantifying the impact each item had on the measurement of general distress. We further specify that participants were healthcare workers involved in a disruptive pandemic, which imposed them unprecedented and heavy workloads coupled with lack pf preparation to cope with such demands. In such circumstances, questions about utility, capacity to make decisions, loss of trust and confidence showed peculiar responses, affecting in different way the psychological wellbeing; feeling useless (Item 3) and thinking of yourself as a worthless person (Item 11) caused more severe impairments than, for instance, feeling constantly under strain (Item 5) or being unable to enjoy day-to-day activities (Item 7).

The analysis on the item response patterns also allowed the classification of subjects according to different impairment levels: the first class with almost all responses equal to 0 (subjects without distress), the second class where percentages of responses equal to 1 were high only for Item 3, Item 5 and Item 9 (subjects with psychological distress) and the third class with huge percentages of responses equal to 1 (subjects with psychological impairment).

Such a classification agreed with previous results obtained by administering several other psychological questionnaires. Indeed, through an item-based latent class analysis, we could determine the screening outcome without considering the other questionnaires, previously part of the first-level evaluation (IES-R, GAD-7).

IRT was a helpful tool for identifying clinically meaningful subgroups in our population, recognizing distinct patient profiles, and tailoring effective interventions, whose importance was already underlined in previous works [34].

Thus, subjects' classification based only on responses to GHQ-12 could potentially simplify workers evaluation. Results show that one step of the evaluation (i.e. second-level) is redundant and may be skipped. According to symptoms' severity, immediate access to specialist evaluation can be planned for those with psychological impairment (Class 3), without testing them through second-level scales; subjects with less severity, i.e. psychological distress (Class 2), will be instead be monitored with a check evaluation after a certain period of time.

Our study is prone to potential biases as self-selection of respondents [35]. We managed to minimize that risk grounding our investigation on the occupational physician health surveillance, obtaining a very high participation rate and minimizing the risk of untrue or uncompleted answers.

We know that our results cannot be generalized, and neither are they comparable with results obtained in different scenarios. The pandemic's consequences directly affected our population, and this exceptional situation should be carefully considered. However, in terms of psychological assessment, our results agree with findings obtained in similar populations of healthcare workers who expressed high levels of GHQ-12 during the COVID-19 pandemic in Italy (e.g., more than 50% above cut-off equal to 3 in Del Piccolo et al. [10]) and in other countries (e.g., 39% of subjects above cut-off equal to 3 in Dai et al. [8]).

5. Conclusions

The GHQ-12 is commonly analyzed and interpreted according to CTT rules and we decided to complement it by performing an analysis based on IRT. As outlined in our work, drawing on the strengths of IRT as an alternative to CTT analyses supported the development of rigorous measures and valuable interpretations. It was possible to classify the degree of severity of psychological impairment by administering only GHQ-12 questionnaire and according to response patterns, focusing on the way in answering each question more than the scored obtained as a sum of "positive responses".

In light of these results, our approach may suggest simplifying the multistep protocol for evaluating mental health in occupational settings, recommending using GHQ-12 as a single measurement tool to be the most effective. Such a method may also meet the need for resources and time reduction when conducting studies and assessments involving workers.

Through such analysis, we gave an example of the utility of IRT in psychometric studies conducted among workers populations. The application of appropriate methodological tools to support the interpretation of questionnaires could sensibly discover their potential in simplifying the screening framework and saving one of the most important workers' resources: their time. Even in questionnaire-based epidemiological studies, in many cases, *less is more*.

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Institutional review board statement: The study was approved by the Hospital Ethical Committee (Milan Area 2 Ethical Committee, n.652_2020 of July 21, 2020) and was conducted in compliance with all local legal and regulatory requirements, Good Clinical Practice, the International

Conference on Harmonisation document and the Declaration of Helsinki.

Informed consent statement: The participation was voluntary; each subject read and signed an extended informed-consent to participate in the study.

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Assessment of Forward Head Posture and Ergonomics in Young IT Professionals – Reasons to Worry?

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Keywords: Neck disability; craniovertebral angle; musculoskeletal disorders; workspace ergonomics; software engineers; COVID-19 pandemic

Abstract

Background: *Prolonged computer use and poor ergonomics among IT professionals are considered risk factors for musculoskeletal disorders. This research aims to analyze the degree of forward head posture and workplace ergonomics in young IT professionals to assess the risk for a neck disability.* **Methods:** *A prospective study was carried out by assessing the sitting posture at work, neck disability in the cervical region, quality of life, physical activity, and ergonomics of the workspace in 73 young IT professionals (32.56±5.46 years).* **Results:** *The score for the cervical functional disability index (NDI) showed a mild neck disability (8.19±7.51). The craniovertebral angle has an average value of 32.01±11.46, corresponding to a light forward head posture, and it positively correlated with age and work experience and negatively correlated with ROSA (r=0.24, p<0.05). The NDI positively correlated with physical activity (r =00.32 p<0.05) and with ROSA (r= 0.24, p<0.05).* **Conclusions:** *In IT professionals, neck disability is associated with the lack of workspace ergonomics and the amount of physical activity. Forward head posture correlated with age, work experience, and poor workspace ergonomics. According to our findings, there are real concerns about the influence of head posture and workplace ergonomics on health among IT professionals. We consider that it is necessary to adopt preventive measures to address neck disability and improve workspace ergonomics.*

1. Introduction

Prolonged use of computers for professional purposes often involves frequent and extended periods at the workplace that are not always ergonomically designed. Moreover, among IT professionals, sedentary activity due to long static periods at the computer affects all body systems [1]. Due to the COVID-19 pandemic, all professional activities have been affected, many of them resorting to teleworking. However, in the case of IT professionals, these changes proved to be unfavorable, being a determining factor in the prevalence of musculoskeletal disorders and cervical pain [2]. Essential aspects in managing and preventing work-related musculoskeletal disorders in the case of IT professionals include postural assessments, workstation ergonomic interventions, and work-break time frames [3, 4].

In the literature, studies of professional computer users show that these static postures seriously impact the functionality of the upper torso and the cervical region, implicitly often identified in posture changes in the sagittal plane [5]. The most

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commonly identified posture in computer users is described by the anterior projection of the head, defined as the anterior position of the head relative to the gravitational line – recognized in the scientific literature as forward head posture [6]. In addition, forward head posture is considered one of the main risk factors in developing musculoskeletal disorders among IT professionals [7, 8].

According to the literature, head posture assessment among computer users is often performed sagittally due to the positioning of the computer workstation (the monitor and auxiliary devices) in the frontal plane [6]. From a clinical point of view, the assessment of postural deficiencies of the head and neck from the sagittal plane should be performed by measuring angles such as the craniovertebral angle (CVA), head positioning angle, head tilt angle, and cranial rotation angle [9].

Recent scientific work considers that the primary method for analyzing the anterior projection of the head is the determination of the craniovertebral angle through photogrammetry [6, 10], which can be evaluated with the help of Posture Screen Mobile software [11, 12].

The means for assessing the workspace ergonomics described in the literature involve various observational methods such as the Rapid Office Strain Assessment (ROSA) checklist [13]. In the scientific literature, several types of questionnaires assess cervical musculoskeletal disorders using patient-reported instruments, the Neck Disability Index (NDI) being the most commonly used for measuring the status of neck pain and the level of disability secondary to pain [14, 15].

This research aims to analyze the degree of forward head posture and the ergonomics of the workplace in young IT professionals to assess the risk for a neck disability.

2. Methods

Informed consent was obtained from all participants involved in the study. We conducted this prospective study between November 15, 2021, and February 15, 2021, in the context of the COVID-19 pandemic.

2.1. Participants

We invited twelve IT companies to participate in the current research by contacting their human resources department; nine of them accepted our invitation. One hundred fifty-two employees received a letter of invitation and the study protocol. Inclusion criteria were:

- Professional activity in the field of IT;
- At least two years of relevant work experience in the field of IT;
- Minimum age of 23 years;
- Written confirmation for participation in the study.

Exclusion criteria were:

- Any history of cervical pathologies independently of the profession, present before the initiation to the study: diagnosed degenerative and inflammatory disorders of the cervical spine (such as spondylosis, ankylosing spondylitis), cervical traumas, and surgical interventions in the cervical area;
- Absence to any of the stages of the study (regardless of the reason).

All volunteers signed informed consent to participate in the study. The local ethics committee approved the study protocol, which respected the Helsinki Declaration.

2.2. Study Protocol

The study protocol was divided into three stages: Stage I – which consisted of a 20 min survey, followed by Stage II – an objective assessment of the sitting posture at work, and Stage III – the evaluation of the workspace ergonomics.

2.2.1. Stage I - Survey Implementation

The survey comprised four sections: (i) demographic data and details about the professional activity; (ii) neck disability assessment; (iii) quality of life; (iv) physical activity assessment.

1. *Demographic data* (gender, age, height, weight, dominant hand) and *details about the professional activity* (work experience, duration of weekly working days, and the average number of hours spent on the computer, place of professional activity – at the office

(within the company) or home (remotely), number and duration of daily breaks, information about the alternation of office position and data about the current state of health).

2. *The neck disability assessment* was performed using the Neck Disability Index (NDI) questionnaire – it contains ten items that refer to neck pain (intensity) and the level of ability to manage daily living activities (personal care, reading, lifting, headache, work, concentration, driving, sleep and recreation) [14]. The NDI score is interpreted as 0-4=no disability, 5-14=mild disability, 15-24=moderate disability, 25-34=severe disability, and over 34= total disability, where a score of 50 converted to percentiles represents 100% [15]. According to Kumari et al., the NDI score is calculated as follows: total score/total possible score, transformed to percentage multiplied by 100=% points [16].

3. *The quality of life* was evaluated by applying the SF-36 quality of life questionnaire composed of 8 scales (36 questions): physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue or vitality, and general health perceptions [17]. The results can vary between 0 and 100, with a higher score representing a better general state of health [18]. The SF-36 questionnaire is frequently used as a valuable tool in determining health status [19].

4. *Physical activity assessment*: the participants' type, frequency, and volume of physical activity.

2.2.2. Stage II - Evaluation of the Sitting Posture at Work

Head and neck posture assessments were performed at the workstation of each participant, either at their home office setup or within the company office by an independent investigator. All images were taken with the same camera placed on a tripod 1.5 m away from the participant and adjusted at shoulder level. The camera recorded a 60 minutes video of the participant during the work time activity. In order to reduce potential false working postures, participants were asked to continue their professional activity while the camera was recording. The video analysis was performed by a second investigator who selected a frame of the most relevant posture (the posture maintained by the participants for the most extended period).

The photographic analysis was done in the second part of the first working day of the week (or immediately after a holiday) to obtain relevant results and implicitly reduce the bias. In addition, we used the Posture Screen Mobile Software (PSM) [11] to obtain accurate and more detailed measurements of the craniovertebral angle and to analyze the head's position.

After selecting the images of all participants, these were uploaded into the PSM software. The height and weight were entered into the PSM software after creating a record of each participant. The digitization process involves specific landmarks that were placed on the lateral view in the following points: the top part of the monitor, the bottom part of the monitor, the lateral canthus of the eye, the correct interior of the external acoustic meatus, the center base of the neck at the cervicothoracic junction, spinous process of the C7 vertebrae, seventh thoracic vertebrae, the center of the thorax – approximately at T6-T8 level, the center of the mid-lower torso at T10-L1 level, elbow, wrist, hand (center of distal metacarpals), the center of the hip - great trochanter, knee - lateral of the tibiofemoral joint and ankle - the center of the malleolus (Figure 1). All points were marked using reflective stickers placed according to the above body landmarks.

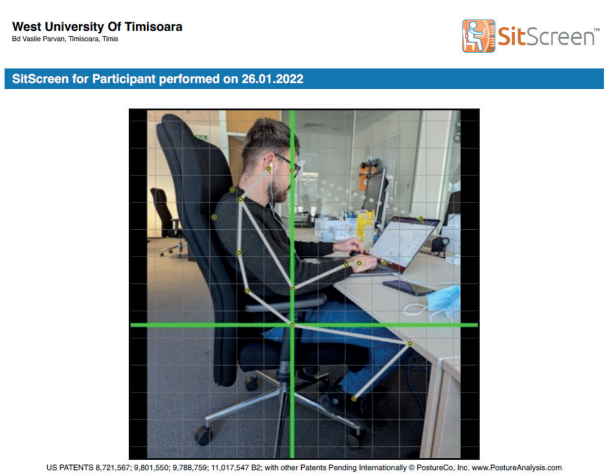

Figure 1. Anatomical landmarks, digitisation process in PSM.

The craniovertebral angle was analyzed with two anatomical landmarks (the spinous process of the C7 cervical vertebrae and the outer part of the ear-tragus). This angle is formed by the horizontal line passing through the seventh cervical (C7) vertebra's spinous process and the line between the C7 vertebra's spinous process and the ear's tragus [20]. According to Shaghayegh Fard et al., values <48-50° of the craniovertebral angle imply a greater rate of occurrence of forward head posture [21]. Therefore, the craniovertebral angle is considered normal when higher than 50°, light when it is between 30°-50°, and severe when it is below 30° [22].

During the process of digitization, the PSM software measures the craniovertebral angle (CVA), head-neck angle (neck flexion angle), head-tilt angle (relative to horizontal), gaze angle, high thoracic angle, neck posture angle, elbow angle, wrist angle, trunk-thigh angle, thigh angle, and lower leg angle. The results obtained using the PSM software present the relation between the sitting posture of the participant and workspace ergonomics.

2.2.3. Stage III - Assessment of the Workspace Ergonomics

The workspace was assessed using an independent investigator's Rapid Office Strain Assessment (ROSA) checklist, blind to the previous evaluation stages. ROSA is an observational method that assesses chair height, pan depth, armrest, back support, duration of sitting, and postures when using the telephone, monitor, keyboard, and mouse, all results producing an overall score that will be analyzed with a scoring chart. A final score higher than 5 implies an increased ergonomic risk factor and a high level of discomfort [13]. Statistical analysis was performed using SPSS Version 26. A bivariate (1-tailed) Pearson correlation test was used to observe the relation between the measured parameters.

3. Results

From the 105 IT specialists recruited in the study, we enrolled 73 (39 men and 34 women). Eight participants were excluded due to medical conditions mentioned in the exclusion criteria, and 24 participants dropped out after the first stage of the study protocol. The demographic characteristics of the group are shown in Table 1.

Due to the COVID-19 pandemic, 33 (45.21%) participants adopted a remote work style and, in some cases, a hybrid mode (remote work combined with office work). Many participants spend, on average, 6-8 hours/day at the computer (n=31, 42.47%). Many participants (n=33, 45.21%) also reported that they work from home (remotely), followed by a large number who adopted a hybrid mode (n=28, 38.36%), whereas only 16.44% (n=12) conducted their professional activity at the office. Among those adopting a hybrid regime, 12.3% worked 1-2 days from home/week, 23.2% worked 2-4 days from home, whereas 47.9% worked 4-6 days a week from home.

Break frequency during a working day was relatively high, with 36.9% stating that they take 3-4 breaks/day, each lasting about 5-10 minutes long (61.6% of the participants).

According to the Occupational Safety and Health Administration (OSHA), sitting still for prolonged periods when working at the computer is unhealthy, and they recommend changing this position frequently.

Sources of information about office ergonomics vary widely. Most participants (n=53, 72.6%) know workspace ergonomics, obtained through online research, specialized courses, ergonomic specialists, friends, colleagues, or social media. The most commonly used device among the IT professionals in our research is the laptop (n=67, 91.78%), with only a few using a computer (n=6, 8.10%). For most of their professional activity, 54.7% (n=40) of the participants used two monitors.

In terms of physical activity, a large number of participants (n=35, 47.9%) stated that they join in physical activities several times a week, and only a

Table 1. Characteristics of the study group.

Parameter	Mean±Standard deviation (n=73)
Age (yrs.)	32.56±5.46
Body Mass Index (kg/m^2)	23.52±3.56
Professional experience (yrs.)	9.32±5.56

few participants (n=4, 5.48%) from the entire group do not join any physical activities. 42.47% (n=31) of the participants stated that they endorse physical activities several times a week with a frequency of 3-4 workouts/week, followed by 27.4% (n=20) with a frequency of 1-2 workouts/week. 15.07% (n=11) of the entire group is sedentary, and 5.48% (n=4) practice high-performance sports. 9.59% (n=7) of the participants have daily physical activities such as walking or cycling to work. For statistical analysis, physical activity was coded with 1 – daily physical activity, 2 – physical activity several times a week, 3 – physical activity several times a month, 4 – physical activity several times a year, and 5 – never.

The correlations between the measured parameters are presented in Table 2. The mean value of the cervical functional disability index (NDI) is 8.19±7.51 (Table 2), which, according to Vernon, represents a mild disability score [15]. The mean craniovertebral angle measured using the Posture Screen Mobile software has an average value of 32.01±11.46 (Table 2).

The craniovertebral angle was positively correlated with age (r=0.28, p<0.01) and work experience (r=0.23, p<0.05) and negatively correlated with ROSA (r=0.24, p<0.05). The head-neck angle was negatively correlated with age (r=-0.26, p<0.05) and with work experience (r=-0.21, p<0.05) and positively correlated with ROSA (r=0.29, p<0.01). The gaze angle was negatively correlated with work experience (r=-0.21, p<0.05) and the device used – laptop/computer (r=-0.22, p<0.05), and positively correlated with ROSA (r=0.21, p<0.05). Finally, the NDI was positively correlated with physical activity (r =0.32 p<0.05) and with ROSA (r=0.24, p<0.05).

4. Discussion

Our study aimed to assess the level of cervical disability among young IT specialists by assessing the relationship between cervical spine posture during professional activities, age, work experience, level of physical activity, and the impact of workspace ergonomics. The results obtained provide valuable information on these topics. In addition, Lamba et al. also confirmed the development of neck and upper limb disabilities among IT specialists using computers more than 40 hours per week [23].

Aegerter et al. noticed that the number of daily breaks and workstation ergonomics could influence the level of neck disability [24]. Therefore, they conducted a longitudinal study starting from 2 hypotheses – neck pain prevalence is influenced by working from home, and workstation ergonomics, break time during computer use. The total amount of time spent at the computer could increase neck pain intensity

Table 2. Descriptive Statistics and 1-Tailed Bivariate Pearson Correlations for Manifest Variables.

	Variables	1	2	3	4	5	6	7	8	9	10	11
1	CVA	-										
2	Head Neck Angle	-0.94**	-									
3	Gaze Angle	-0.35**	0.32**	-								
4	Thorax Angle	-0.06	0.12	0.00	-							
5	Age	0.28**	-0.26*	-0.19	0.04	-						
6	Neck Disability Index	-0.06	0.13	0.19	0.06	-0.15	-					
7	Work Experience	0.23*	-0.21*	-0.21*	0.10	0.87**	-0.08	-				
8	Gender	-0.10	0.13	0.02	0.00	-0.05	0.02	0.02	-			
9	Physical Activity	-0.13	0.06	0.04	-0.02	-0.05	0.32*	-0.09	0.11	-		
10	Device Type	-0.13	0.10	-0.22*	-0.01	0.06	-0.09	0.09	0.14	0.13	-	
11	ROSA	-0.24*	0.29**	0.21*	0.00	0.01	0.24*	0.00	-0.11	0.04	.17	-
	Mean	32.01	57.02	19.49	157.99	32.56	8.19	9.32	1.53	2.32	1.06	3.37
	SD	11.46	11.57	11.15	15.37	5.46	7.51	5.56	.50	.87	.25	.87

*M=mean; SD=standard deviations; *=p<0.05; **=p<0.01.*

and neck disability. For their study, they collected data before the COVID-19 pandemic started and made a follow-up during the lockdown. The findings of their study show that a higher number of breaks during computer use could reduce the degree of a neck disability and that there is an association between neck pain intensity and the number of hours spent at the computer.

We have chosen to evaluate the forward head posture by measuring the craniovertebral angle as per the findings of Kim & Kim, who stated that this method is reliable when investigating the functionality of the neck region [25]. In addition, recent scientific work considers the primary method for analyzing the anterior projection of the head by determining the craniovertebral angle using photogrammetry as a validated, reliable, and objective method [6, 10, 20]. Following the posture's photographic analysis, the craniovertebral angle measurement can be done with the help of Posture Screen Mobile [11, 12], a non-invasive, easy-to-use, and portable way that allows optimal assessment and does not require experience in obtaining accurate and reliable measurements.

According to the study by Szucs & Brown, the Posture Screen Mobile software has strong reliability and validity in scientific research and for clinical purposes [12]. Natural numbers with finite decimals represent the result of the measured craniovertebral angle when using the Posture Screen Mobile app. A study by Boland et al. showed that postural assessments analyzed with the PSM software are clinically relevant, especially when diagnosing the forward head posture [11]. Other scientific studies assessing poor postures among computer users, implicitly the forward head posture, by measuring the craniovertebral angle, concluded that the photogrammetry technique analysis using the PSM software is reliable and conclusive [26, 27]. The equipment chosen and the assessment method applied were considered unobtrusive/non-invasive and feasible in the COVID-19 pandemic context.

Even though the mean age of the studied group indicated a relatively young group (32.56±5.46 years), we noticed that the CVA degree is positively correlated with age and work experience, consistently with the findings of Sun et al. [28].

Implicitly, some misalignments can be noticed with a poor posture, such as an anterior projected head. According to Hansraj, as the weight of the head is shifted anteriorly in the forward head posture, not only the craniovertebral angle worsens/is affected, but it also changes and can be seen in the gaze angle, dropping below the horizontal line – which is considered to represent a level of comfort. Our study has identified significant results when correlating parameters such as the CVA, gaze angle, and head-neck flexion angle [29].

Nejati et al. conducted a study regarding the relationship between poor postures (forward head posture) and the prevalence of cervical pain, respectively the degree of cervical disability, in two groups of participants (a symptomatic group with cervical pain and an asymptomatic group without cervical pain)[30]. Following the measurements of the craniovertebral angle, the differences between the symptomatic and asymptomatic groups were minor (UCV=23.00±0.70 in the symptomatic group, respectively UCV=28.40±12.40 in the asymptomatic one). The study concludes that the value of the craniovertebral angle does not directly influence the degree of cervical disability and, implicitly, by the degree of forward head posture.

In compiling the online survey, we chose both the Neck Disability Index and SF-36 as per the results of Pontes et al., which show that these are reliable and valid tools for evaluating disability and neck pain [31]. In addition, a review conducted by Bobos et al. demonstrated that the Neck Disability Index questionnaire has from moderate to excellent level of reliability in test-retest and is supported by the qualitative results of the content [32]. Although the Neck Disability Index was published first in 1991 by Vernon et al., the only change that has been made was the word “neck” that was added to the term “pain” to specify that the question referred to the “neck pain” of the individual taking the survey. The scientific literature regarding ways of treating and preventing neck pain, and, all the more, neck disability, highly recommend specific exercises that follow outcomes, such as strengthening or stretching the involved region. In our study group, participants more involved in physical activities had a lower level of neck disability, the NDI being correlated to physical activity.

According to Lindegård et al. [33] and Jun et al. [34], the NDI can be influenced by multifactorial causes, such as ergonomic risk factors, psychosocial factors, and individual factors. A specific method of assessing ergonomic workplace risk factors among computer users is the Rapid Office Strain Assessment (ROSA) checklist published by Sonne & Andrews [13], and according to the findings of Panchal et al., it is highly applicable among IT specialists [7].

Our results support Sonne et al., who demonstrated a relationship between the level of discomfort and a higher ROSA score; in our study, significant correlations were noticed between the ROSA score and NDI [35]. Our conclusions are also consistent with the findings of Aegerter et al., i.e., that neck disability can be positively influenced by increasing the number of breaks during computer use and when physically active [24], and with those of Barkhordarzadeh et al., suggesting that great focus should be oriented towards an ergonomic intervention, to reduce work-related musculoskeletal disorders and cervical disability [36].

The use of the questionnaire method is considered an appropriate approach in scientific research because it allows the collection of a large amount of information by obtaining accurate and easily measurable data in the shortest possible time and with the least possible need for resources; however, there are disadvantages such as a low response rate and a high level of subjectivity on the part of the participants. Nowadays, the vast majority of IT specialists are working remotely, which, according to scientific literature findings, can harm them. Out of 73 participants, only a small number do not know if they change their position (13.6%) or do not change it during a working day.

Strengths and Limitations

To our knowledge, this is the first study that uses the Posture Screen Mobile software to assess the craniovertebral angle in IT specialists. We consider our method to be not only non-invasive but also highly applicable in the case of remote workers. Furthermore, we consider our survey to be original in its approach, as we did not find any other study analyzing the correlation between neck disability, quality of life, and workspace ergonomics.

The study has the following limitations: the self-reported data obtained in the first stage of the study protocol cannot be independently verified; in the second stage of the study protocol, the participants' posture could have been influenced by the awareness that they were video-recorded. Also, we consider that recording the posture during work time for a more extended period, in different timeframes of the working day and the week, would lead to more relevant results.

5. Conclusion

In IT professionals, the degree of neck disability is associated with the lack of workspace ergonomics and the amount of physical activity. The forward head posture positively correlates with age, work experience, and poor workspace ergonomics. According to our findings, there are real concerns about the influence of head posture and workplace ergonomics on health among IT professionals. We consider that it is necessary to adopt preventive measures to address neck disability and improve workspace ergonomics.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by approved by The Scientific Council of University Research and Creation by West University of Timisoara (approval number: 62876/ November 11, 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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

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Using Structural Equation Modelling to Predict Safety and Health Status among Stone Industries

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Keywords: Organizational structure; safety and health; structural equipment modelling; stone industry

Abstract

Background: *The creation of a working organization with a high safety level facilitates the employees' health in their workplaces; therefore, the current study evaluated the effect of the organizational structure on safety and health in the stone industry.* **Methods:** *This study was conducted among 100 stone industries in Isfahan, Iran. The participants were requested to complete the organizational structure questionnaire and ELMERI checklists. Smart PLS 3.0 used to test the hypothesis.* **Results:** *The model fit index showed the standardized root mean square (SRMR=0.08), the normalized fit index (NFI=0.9), the coefficient of determination (R2=0.362), effect size (f2 was less than 0.2), and the Predictive relevance of the model (Q2=0.216) which is considered a good fit for mode. In addition, the relation between formalization and health and safety was significant (β=-0.47).* **Conclusions:** *The findings suggest that organizational factors are the basic reasons for occupational accidents and the main indicator of safety and health performance.*

1. Introduction

The modern economy is led by agriculture, manufacturing, and services. Regardless of the deciding factors, each country's economic growth and improvement based on a weak labour protection system is an invitation to accidents [1]. In the European Union (EU), more than 5,500 people die annually from workplace accidents. Based on the estimates by the International Labour Organization, 159,000 people in the EU lose their lives annually as result of occupational diseases. Companies in the EU lose about 143 million working days because of workplace accidents annually. All these injuries, deaths and occupational diseases cost the EU economy at least 490 billions euros annually [2]. Occupational safety and health in working groups at the workplace play a basic role in successful business management in many studies [3]. Arthur Schopenhauer, a German philosopher (1788-1860), emphasized health importance and stated, "Health is not everything, but without health, everything is nothing" [4]. Hence, the definition of health and safety and integration of these terms can be considered occupational health and safety and a holistic approach to staff's welfare in the workplace. According to

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WHO's definition, occupational health involving occupational hygiene, occupational medicine, safety, physiotherapy, rehabilitation, occupational psychology, ergonomics, etc. Safety, on the contrary, is defined as safeguarding a person from physical harm. International Occupational Health Association defines Occupational Safety and Health (OSH) as the science of anticipating, evaluating, and controlling hazards arising in or from the workplace that could impair the health and well-being of workers [5, 6].

Regarding workplace safety issues, some researchers say that each workplace has a specific environment, which may indirectly affect the industry's accident rate, e.g., decisions made in politics and management, leadership and management skills, education level, mutual communications, etc. [7, 8], are under the employer's responsibility. On the other hand, the employer or industry management is responsible for this area based on industry safety rules and workplace protection. Therefore, OSH requirements must be inseparable from modern industries' performances [2]. In addition, many papers written by famous management theorists (Frederick W. Taylor, Henry L. Gantt, Frank and Lilian Gilbreth, Henry Fayol, Hugo Münsterberg, George E. Mayo, and others) explain that the interests of workers, managers, and owners must be matched and aligned [9]. Hence, organizational improvement is among the crucial elements of occupational safety. Creating a working organization with a high safety level ensures employees' health in their workplaces, so fewer staff leave their jobs or decide to change their occupations. In this case, employees become satisfied, which leads to higher individual and organizational performance and productivity. In this case, the organization achieves its organizational goals.

1.1 Research Hypotheses

Proposed Research Model and Hypotheses Based on the above theoretical assumptions is schematically illustrated in Figure 1. The following hypotheses are formulated: (i) H1: Complexity is positively related to health and safety in the stone industry; (ii) H2: Formality is positively related to health and safety in the stone industry; (iii) H3: Concentration positively affects health and safety in the stone industry.

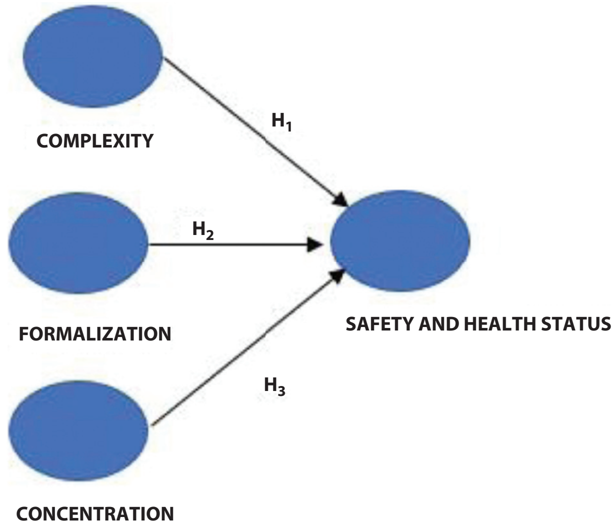

Figure 1. The study conceptual model.

2. Methods

2.1 Data Collection, Participants, and Study Design

This cross-sectional study was conducted among the 100 stone industries in Isfahan, Iran. Data collection started on 1 January 2019 and ended on 28 June 2019. Participants were employees and employers. The selected participants were requested to complete the questionnaire. Participants completed the OSQ and ELMERI checklists and provided demographic information from the work system. Of the 100 questionnaires, 10 did not return measurements or contained more than 20% missing data. This study used statistical frequency analysis to determine central trend measurements (mean) and variance measurements (standard deviation). We tested the research hypothesis using structural equation modelling.

2.2. Instruments

We used the ELMERI checklist developed by the Finnish Institute of Occupational Health (2000) to measure safety and health status. The result is calculated as a percentage. The level safety performance index is classified into four levels: good (75 to 100%), medium (50 to 75%), poor (25 to 50%), and very poor (0 to 25%) [10].

Stephen Robbin's questionnaire was applied to measure organizational structure [11]. This questionnaire has 24 questions, 5-choice, with scores from 1 to 5 in three subscales of complexity, formality, and concentration. The increase in scores in this questionnaire indicates the increase in the scores of each of the subscales of organizational structure. The validity of the questionnaire was measured using Cronbach's alpha coefficient and was evaluated as 0.725 [12].

As shown in the Conceptual Framework (Figure 1), the dependent variable for this study is health and safety, and the independent variables are complexity, formalization, and concentration.

"Health and safety status" is selected as an exogenous latent variable. Therefore, "unsafe behaviors of the worker", "order and tidiness", "machine safety", "industrial hygiene", "ergonomic", "walkways", and "fire and health aid" are selected as the endogenous latent variables. These latent variables include one observable indicator of "unsafe worker behavior", four indicators for "order and tidiness", "machine safety", "ergonomics", and "fire and health aid". In addition, three indicators of "walkways" and five indicators for "Industrial hygiene", complexity, formalism, and concentration are defined as endogenous latent variables. These include 7 observable indicators of complexity and formalism and 10 observable indicators of concentration.

2.3 Statistical Analysis

Karl G. Jöreskog (1935) defines causal modelling as a linear structural, relational model comprising a structural and a measurement model. Structural models elaborate on the association among the latent variables via a series of linear equations. However, the measurement model explains the unobservable measurement of latent variables with the observable predictors or manifest variables, allowing the measurement characteristics of the indicators to be evaluated (Lomax, 1982, 1983) [13-15].

The database turned into Smart PLS 3.0 (https://www. smartpls.com/smartpls3), and the study's hypotheses were tested with the bootstrap method. Since few data had been available, PLS-SEM turned into employed. The technique of statistics evaluation with PLS-SEM for verifying the theoretical version was achieved in 2 steps.

The first step was to evaluate the quality of the measurement model. Various indicators were employed in the analysis of the measurement model, depending on the type of indicator in the model. We used the indicator weights to determine which indicators to remove and which to keep in the model [16]. The measurement model was analyzed based on the developed criteria for the reflective method, convergent validity; internal consistency; and discriminant validity. The standards of convergent validity and internal consistency are suggested by [17]. The validity of the convergence of the reflection structure was verified by the external load and the extracted mean-variance AVE; its value should be more than 0.5. Internal consistency was confirmed by Cronbach's alpha factor composite reliability and rho_A factor. Cronbach's alpha factor measures reliability based on the correlation between the index variables, and composite reliability considers the various loads of these variables [16]. Diagonal elements must be significantly greater than the corresponding row and column off-diagonal elements to achieve proper identification validity [18, 19].

Then measuring the Inner Structural Model outcomes comes afterward, which comprises observation of the model's predictive relevancy and the association between the constructs. The coefficient of determination (R2), Path coefficient (b value) and T-statistic value, Effect size ($f2$), and the Predictive relevance of the model (Q2) are the key standards for evaluating the inner structural model [17].

3. Results

3.1. Assessment of Measurement Model

According to the least square's structural equation modelling, the measurement model was initially assessed by employing Smart PLS 3.0. The convergence validity, discriminant validity and reliability of the measurements used were evaluated to analyze the measurement model.

Table 1 shows that loading above 0.4 on each variable is considered significant. Indicators that have very low loadings below 0.40 must be removed.

Table 1. Measurement model for the research constructs.

Subscales			Factor loading	Cronbach's α>0.7	AVE>0.5	CR>0.7	rho_A>0.7
Safety & health status		Safety behavior	0.871	0.897	0.653	0.926	0.927
		Order and tidiness	0.725				
		Machine safety	0.335				
		Industrial hygiene	0.875				
		Ergonomics	0.877				
		Walkways	0.953				
		Fire and health aid	0.858				
Organization structure	*Complexity*	P1	0.809	0.678	0.598	0.846	0.894
		P2	0.833				
		P3	0.675				
		P4	0.615				
		P5	0.845				
		P6	0.875				
		P7	-0.720				
	Formalization	R1	0.843	0.924	0.703	0.941	0.946
		R2	0.902				
		R3	0.914				
		R4	0.897				
		R5	0.836				
		R6	0.491				
		R7	0.903				
	Concentration	T1	0.828	0.924	0.703	0.941	0.946
		T2	0.794				
		T3	0.785				
		T4	0.791				
		T5	0.826				
		T6	0.84				
		T7	0.836				
		T8	0.797				
		T9	0.853				
		T10	0.812				

Table 2. Discriminant validity: Fornell-Larcker criterion test.

	Complexity	Formalization	Concentration	Safety and health status
Complexity	0.773			
Formalization	0.824**	0.838		
Concentration	-0.779**	-0.864**	0.816	
Safety and health status	-0.479**	-0.593**	0.560**	0.808

No indicators were below 0.40, and as a result, no indicators were deleted. All of the AVEs are above 0.50, which is the recommended cut-off value. The composite reliability for all variables is above 0.60, which is the acceptable cut-off value. So, the measurements employed in this research for each variable are considered reliable.

The Discriminant validity was analysed by employing the Fornell-Larcker criteria. Table 2 represents the Fornell-Larcker criterion comparing the correlation between constructs with the square root of the AVE for each construct.

3.2 Model Fit Test

PLS-SEM does not have a global goodness of fit index. To date, important thresholds are not fully understood. Therefore, a bootstrap and blindfold approaches are implemented to solve these issues. Moreover, these analyses, testing the reliability and validity of the measurement model, are conducted in the first step. The goodness of fit index is usually not shown. However, some researchers have proposed a Standardized Root Mean Square residual (SRMR) and a Normalized Fit Index (NFI) as performance metrics to assess model fit without model specification errors. It is regarded appropriate if the SRMR is less than 0.10 or 0.08 and the NFI range is 0 to 1 (close to 1). In this study, the SRMR was 0.08, considered acceptable. Moreover, the NFI was approximately 0.9, which is considered a good fit for our mode.

3.3 Measuring the Value of R^2

The coefficient of determination measures the model's predictive accuracy because it measures the size of the overall effect and variance described in the structural model's endogenous construct. The R2 value in Figure 2 indicates that the combined three factors of concentration, complexity, and formalization account for 36.2% of the variance in satisfaction. (R2=0.362). See R2 classification by Hair et al. [17]. The power of these factors to safety and health can be explained between the weak and the moderate.

3.4. Estimation of Path Coefficients (β) and T-statistics

Partial least squares statistical significance was determined using resampling techniques such as bootstrap. This procedure provides t-test results for all pass coefficients. The model's path coefficients (β) and t-statistics were used to evaluate the relationship between the independent and dependent variables. The beta coefficient of the structural model between formalization and health and safety was significant, with a p-value of 0.01 and β=-0.47 [20, 21]. See table 3 for more.

3.5 Effects Sizes for Path Coefficients (f^2)

The effect size of the path coefficient between independent and dependent construct (f2). Effect size is a change in R-squared (R2) examined to determine if the effect of the independent structure on the dependent structure has a significant effect (f2), which is automatically calculated by the Warp PLS-SEM software. According to Cohen (1988), the effect size between formalization and health and safety conditions was less than 0.2, which was regarded as small effect [22].

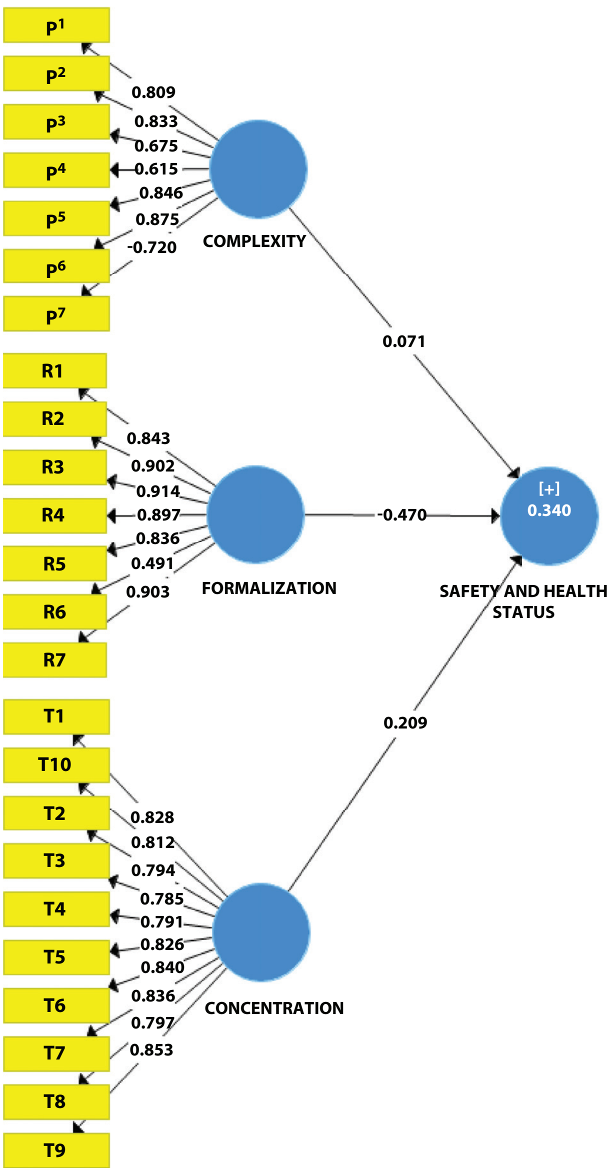

Figure 2. SEM Model for the relationship between safety and health status and organization structure dimensions.

3.6. Predictive Relevance of the Model (Q^2)

The model's accuracy can be evaluated using predictive validity (Q2). This is also known as the Stone-Geisser indicator or redundancy of cross validity (Q2). The Q2 criteria recommend that the conceptual model be able to predict the latent structure. In SEM, the measured Q2 value must be greater than zero for a particular endogenous latent structure [23]. The result shows that the Q2 value for this study model is equal to 0.216. This is above the threshold and confirms that the predictive relevance of the path model of the endogenous construct is valid.

4. Discussion

According to the model's results, there was only a significant and direct relation between the formality of organizational structure and safety. Cox and Cheyne (2000) and Mearns et al. (2003) express that safety rules and regulations have a crucial role in safety level management in organizations [24, 25]. Moreover, Otieno et al. (2019) explain that increased occupational accidents reduce firm performance and show that safety and health regulations moderates the relation between occupational accidents and firms' performance, so they act as a moderator [26]. However, Patel and Jha (2016) indicated that safety regulation had no considerable effect on the safe behaviors of workers [27]. So, Patel and Jha (2014) implanted safety regulations and procedures as the less important determinants of safe work behavior. Fielder's theory (1983) debates that human resources actions affect organizational performance only if they are subjected to strategic policy. In other

Table 3. Path coefficient (β), T-statistics, and P-value.

Hypothesized Path	Standardized Beta	T-Statistics	p Values
Complexity → Safety and health status	0.071	0.496	0.6
Formalization → Safety and health status	-0.47	2.555	0.01
Concentration → Safety and health status	0.2	1.3	0.19

words, effective OSH performance in those corporations that decrease occupational accidents to enhance firm performance requires vertical integration of OSH regulations.

Aliabadi et al. (2018) explain that although unsafe actions of workers are usually introduced as the main reason for industrial accidents, humans are just one of the components in complex systems. Hence, the whole system must be considered to detect accidents source. Aliabadi et al. pointed out that organizational deficiencies do not have a direct impact on unsafe behavior by workers [28]. Other studies have shown that organizational factors such as lack of safety management, organizational involvement, and unsafe regulations directly influence hazardous worker behaviour [29, 30]. In addition, Hoła and Nowobilski (2019) assert that most accidents occur in small- and medium-sized firms that do not have a regular and systematic organizational structure. Because owners and their family members work in such corporations and there is high employee turnover in these firms, many employees leave their jobs every year, and new employees are recruited [31]. These employees do not have sufficient professional experience, so the mentioned reasons result in high occupational accident rates in these firms.

5. Conclusion

Organization factors and organizational structure-related factors are the most basic reasons associated with occupational injuries and accidents and the main indicator of safety and health performance. These variables may, in turn, cause work safety enforcement and problems or indirectly affect occupational accidents and injuries under the influence or in interaction with other factors.

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Respiratory Findings in Herd Dairy Farmworkers from the Nile Delta Region

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Keywords: Dairy; dust; farmworkers; lung functions; respiratory findings; ventilatory

Abstract

Background: *Dairy farmworkers are exposed to a variety of respiratory hazards, including organic and inorganic dust, allergens, disinfectants, and gases emitted by cows and their wastes resulting in a range of adverse health effects. In Egypt, large herd dairy farms (>1,000 cattle) are growing in both size and number and thereby more workers are employed. However, there is a lack of studies on the respiratory health status of these workers. Accordingly, the present study aimed to determine the prevalence of respiratory problems, assess ventilatory functions, and highlight the predictors of abnormal spirometry patterns among Egyptian dairy farmworkers.* **Methods:** *A cross-sectional study was carried out on 282 male workers, of whom 141 were dairy farmworkers and the other 141, not involved in livestock handling, were enrolled as controls. Full history, clinical examination, and ventilatory function measurements were done for both groups.* **Results:** *Dairy farmworkers had a significantly higher prevalence of respiratory symptoms (throat irritation and/or sore throat, cough, sputum production, and difficulty breathing) than controls as well as bronchitis, wheezes on chest auscultation, and obstructive ventilatory patterns. Older age (>37 years), longer smoking duration (>10 years), and longer working duration (>4 years) were independent predictors of abnormal spirometry patterns, particularly obstructive patterns, in dairy farmworkers.* **Conclusions:** *Large herd dairy farms, despite being open and naturally ventilated, are hazardous to workers' respiratory health. Hence, the provision of personal protective equipment, periodic spirometry examinations as well as mandatory breaks and days off, are highly urged.*

1. Introduction

The global dairy industry is one of the most important sectors for combating food and nutritional insecurities, particularly on the African continent [1]. Accordingly, dairy farming in recent years has transitioned from small farms to larger ones breeding thousands of dairy animals and employing a larger workforce [2]. Airborne respiratory hazards, such as inorganic and organic particulate matter, vapors, gases, and fumes, are common in a range of occupational settings and are associated with the development of chronic work-related respiratory diseases [3]. Previous studies have increased our understanding of the various exposures in agricultural environments [4, 5, 6, 7, 8, 9]. Consequently, the respiratory health of dairy farmworkers has gained greater attention in the last decade, after being shown to have higher-than-expected proportionate mortality ratios for respiratory diseases. Dairy

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farmworkers are exposed to a complex range of respiratory hazards including inorganic and organic dust, allergens, fungi, disinfectants, smog-forming volatile organic compounds, and gases emitted by cows and their wastes, such as hydrogen sulfide, methane, and ammonia. Of these, organic dust is considered the most important clinically due to its pro-inflammatory properties [5, 10, 11, 12, 16].

Organic dust is a mixture of air-suspended particles derived from plants, animals, and microbes. On dairy farms, fecal matter, urine, animal feed, animal dander, and hair are common sources of organic dust. Inflammatory and allergic agents, including fungal spores, bacteria, viruses, and pollen, can be found in dust, in addition to microbial-associated molecules, such as endotoxins (from gram-negative bacteria), glucans, muramic acid (from gram-positive bacteria), and peptidoglycans [13].

Inhaled dust is treated as foreign material and can induce either inflammation or toxic reactions resulting in a range of adverse respiratory health effects including nonallergic flu-like illness, organic dust toxic syndrome, asthma, irreversible chronic bronchitis, and reduced lung functions, with a variety of symptoms, such as nose and throat irritation, chest tightness, cough, shortness of breath, and wheezing [14, 15, 16].

Despite technological advances in the dairy industry, the overall exposure of dairy farmers to airborne organic dust, comprising microbial agents, allergens, ammonia, and other gases remains high and represents a serious health hazard. Accordingly, the incidence and prevalence of work-related respiratory diseases, including asthma, chronic bronchitis, upper respiratory tract symptoms, as well as hypersensitivity pneumonitis have remained high [17, 18]. In Egypt, a previous study assessing the prevalence of work-related asthma (WRA) among Egyptian adult agriculture workers in great Cairo reported that 11 out of 150 (7.3%) workers had WRA with a statistically significant difference in FEV1, and FEV1/FVC ratio observed between the WRA and non-WRA groups [19].

There are approximately 134 large Egyptian farms with an average herd size of 3,100 cattle predominantly located in the Delta region and around Nobaria. These farms can be described as "business farms" as most of the work is performed by employees and the main aim of these enterprises is to generate an expected return on investment [20]. We are not aware of previously published research on the respiratory health consequences of working on large herd Egyptian dairy farms, despite the continued growth of these farms in both size and number. Accordingly, greater numbers of workers are being employed with limited access to health services. Hence, the present study aimed to determine the prevalence of respiratory problems and assess ventilatory functions among Egyptian dairy farmworkers. The secondary aim was to highlight the predictors of abnormal spirometry patterns.

2. Methods

2.1 Study Design and Setting

A cross-sectional study was conducted on three large (>1,000 cattle per farm), as defined by the Food and Agriculture Organization [FAO] [21], open, naturally ventilated, privately owned dairy farms in Gamasa City, Dakahlia Governorate in the Eastern Nile Delta region of Egypt from April 1, 2021, to October 31, 2021. These farms operated 24 hours a day, 7 days a week. The produced milk was sold to large-scale dairy plants to manufacture pasteurized milk and dairy products that were distributed across Egypt. The farms were chosen due to convenience as the owners had agreed to provide informed consent after being informed of the study's purpose and procedures. Furthermore, they had a large workforce that enhanced the study's conduction and data collection.

2.2 Study Population

Participants were divided into two study groups: (i) The exposed group, consisted of male dairy farmworkers that worked daily in weekly rotating shifts. Each participant was responsible for performing a specific task throughout his shift including mechanical milking (parallel type), mixing feed and feeding cattle, routine veterinary care, birthing, breeding/caring for calves, moving cattle, scraping/removing manure (primarily by loader trucks and tractors), as well as administration and supervision. The second group (ii) was the control group and comprised participants recruited from service and office workers employed in different governmental offices in Dakahlia Governorate with no previous or current history of contact with livestock. Groups consisted of equal numbers of participants matched by age, gender, residence, and education.

2.3 Sample Size

The sample size was calculated using Open-Epi software [https://www.openepi.com/SampleSize/SSPropor.htm] based on the results of an earlier study [22], in which the prevalence of cough was 25.0% among male dairy farmers and 9.6% among office workers as controls. Using a 95.0% confidence level, and 80.0% power, the sample size was calculated as 107 participants for each group. Taking into account a non-response rate of 10.0%, the sample size was increased to 118 individuals. The total workforce in the three dairy farms, where the study was conducted, was 180 male farm workers. Of these, 160 workers agreed to participate (a response rate of 88.9%). Nineteen workers out of 160 were excluded after applying the study inclusion and exclusion criteria, leaving 141 workers eligible to participate. Inclusion criteria were adult workers aged 18 and above, that had worked on the dairy farm for at least a year. To avoid misinterpretation of spirometry results, participants with a history of COVID-19 infection, which was pandemic at the time of the study, were excluded.

2.4 Study Tools

Face-to-face interviews were conducted using a pre-designed questionnaire developed after reviewing relevant literature [2, 5, 12, 14]. The questionnaire was divided into four parts: (i) personal history involving age, gender, educational level, residence, marital status, and smoking history; (ii) current occupational history including nature of the job, working duration (years), hours of daily work, number of days worked per week, shift work and its type, breaks during working shifts, use of machinery (milking machine, loader trucks, tractors and/or feeder mixers), personal protective equipment (PPE) usage and type, keeping livestock in their homes and additional jobs besides the current job; (iii) previous occupational history involving place, nature, and duration of previous occupations; (iv) respiratory symptoms were assessed using the American Thoracic Society-division of lung disease [ATS-DLD] standardized questionnaire which included queries about the presence of cough, sputum, breathlessness, wheezing, and previous history of respiratory health problems (pneumonia, tuberculosis, bronchitis, asthma, or chest injury) [23].

Clinical examination was carried out on all study participants with an emphasis on local chest examination to detect clinical signs of respiratory problems through inspection, palpation, percussion, and auscultation for abnormal breathing or additional sounds. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Normal weight, overweight, and obesity were defined as a BMI of (18.5-24.9 kg/m^2), (25.0-29.9 kg/m^2), and (≥30 kg/m^2), respectively [24].

For Ventilatory Lung function testing, a portable calibrated spirometer with a built-in computer program [SpiroLab III, MIR, Italy], was used to assess ventilatory lung function parameters with adherence to the American Thoracic Society guidelines [25]. Participants were asked to sit upright, inhale maximally, and then maximally exhale into a disposable mouthpiece attached to the spirometer with the nose clipped, or the nostrils should be manually closed, to allow airflow to and from the lungs only through the mouthpiece with the lips tightened around the mouthpiece to prevent air leakage. The procedure was repeated three times with adequate rest between measurements (≥30 seconds). The best of the three values was recorded. The measured lung-function parameters were FVC (forced vital capacity), FEV1 (forced expiratory volume in one second), and FEV1 /FVC ratio (the fraction of air exhaled in the first second relative to the total volume exhaled). These were read off the spirometer screen. Participants were advised not to smoke or perform any vigorous exercise for at least one hour before testing, not to eat a large meal two hours before testing, and not to wear tight-fitting clothing [26]. FEV1, FVC, and FEV1 /FVC were expressed as percentages of predicted values based on age, gender, ethnicity, weight, and height parameters. The interpretation was performed according to the American Thoracic Society/European Respiratory Society guidelines (ATS-ETS), which use the lower limit of normal (LLN) as a cutoff. The LLN is defined as less than the fifth percentile of spirometry data obtained from the third national health and nutrition examination survey (NHANES III) [27]. When the measured FEV1 /FVC ratio was less than the LLN of the corresponding predicted value and the measured FVC was more than the LLN value, participants were assumed to have airway obstruction. Lung restriction was defined as an FVC of less than the LLN value and an FEV1 / FVC ratio greater than or equal to the LLN. Finally, a mixed pattern of abnormal ventilatory function was considered when both the FEV1 /FVC ratio and FVC were less than the LLN [28]. Precautionary measures for conducting spirometry during the COVID-19 pandemic were taken according to the recommendations of Crimi et al. [29].

2.5 Study Workflow

Dairy farmworkers were interviewed and examined in the farm manager's office during the working day at times suitable to them without interrupting farm operations. For the control group, interviews and examinations were conducted in the director's office. Study visits were conducted 2-3 times weekly, with an average of 8-10 subjects evaluated per visit. The questionnaire was completed first, followed by a clinical examination, and then ventilatory function measurements with 20-30 minutes between each.

2.6 Statistical Analyses

Collected data were analyzed using Statistical Package for Social Sciences version 28. Categorical data were presented as numbers and percentages. The Chi-square test, Fisher's exact test, and Monte Carlo test were used for comparisons between groups, as appropriate. Numerical data were presented as mean ± standard deviation if parametric or the median (minimum-maximum) if non-parametric. The independent sample t-test was used to compare parametric variables and the Mann-Whitney test was used to compare non-parametric variables between groups. A binary stepwise logistic regression analysis was used to detect independent predictors of abnormal spirometry patterns as dichotomous outcome variables. Using the forward (Wald) method, significant predictors in the bivariate analysis were entered into the regression model. Adjusted odds ratio (OR) and corresponding 95% Confidence Interval were calculated. P values less than 0.05 were considered statistically significant.

3. Results

In the present study, 53.2% of dairy farmworkers were below 37 years of age with a mean age of 35.8±10.7 years while 54.6% of the control group were 37 years of age or older with a mean age of 37.8±6.2 years (Table 1). The majority of dairy farmworkers and the control group were married (73.8% and 77.3%, respectively) and rural residents (81.6% and 75.9%, respectively). More than three-quarters of dairy farmworkers and the control group were educated to secondary school levels and above (84.4% and 87.2%, respectively).

Less than half of dairy farmworkers (41.1%) and the control group (34.8%) were current smokers, with cigarette smokers accounting for the majority of current smokers in both groups (93.1% and 85.7%, respectively). Dairy farmworkers reported smoking for a longer duration (10 years) than the control group (6.5 years), with a median of 9 and 8 cigarettes smoked per day by dairy farmworkers and the control group, respectively. More than half of the dairy farmworkers had a normal weight (53.9%) while approximately half of the control group were overweight (50.4%).

Regarding occupational parameters (Table 1), the median working duration of dairy farmworkers was 4 years with a mean number of hours worked by the week of 72.5±22.0 hours. Among dairy farmworkers, (31.9%) were parlor workers followed by veterinary workers (23.4%) and feeders (22.0%). The majority of dairy farmworkers worked in rotating shifts (92.2%), with more than two-thirds taking breaks during working shifts (71.6%). Less than

Table 1. Personal characteristics of the studied groups and occupational profile of dairy farmworkers.

	Dairy farmworkers (n=141)		Control group (n=141)		
Personal characteristic	**No.**	**%**	**No.**	**%**	**p-value**
Age, y (Mean±SD)	35.8±10.7		37.8±6.2		0.052
Married	104	73.8	109	77.3	0.489
Unmarried[a]	37	26.2	32	22.7	
Rural Residence	115	81.6	107	75.9	0.244
Urban Residence	26	18.4	34	24.1	
Illiterate/ read and write	11	7.8	8	5.7	0.745
Basic Education	11	7.8	10	7.1	
Secondary degree and above	119	84.4	123	87.2	
Current Smoker	58	41.1	49	34.8	0.389
Ex-smoker	6	4.3	4	2.8	
Nonsmoker	77	54.6	88	62.4	
Smoking[b] Cigarettes	54	93.1	42	85.7	0.233
Smoking[b] Shisha	0	0.0	2	4.1	
Cigarettes and shisha	4	6.9	5	10.2	
Years smoking[c] Median (range)	10 (1-40)		6.5 (2-15)		0.087
Cigarettes/day, Median (range)	9 (2-30)		8 (2-20)		0.350
BMI Normal	76	53.9	68	48.2	0.062
Overweight	57	40.4	71	50.4	
Obese	8	5.7	2	1.4	

	Dairy farmworkers (n=141)	
Occupational characteristic	**No.**	**%**
Years with the job, Median (range)	4 (1-30)	
Working hours/week, Mean±SD	72.5±22.0	
Parlor workers	45	31.9
Veterinary workers	33	23.4
Feeders	31	22.0
Drivers	12	8.5
Veterinary doctors	5	3.5
Others [d]	15	10.6
Rotating shift work [e]	130	92.2
Breaks during working shifts	101	71.6
Use of machinery at work [f]	32	22.7
Personal protective equipment (PPE) usage	88	62.4

Table 1. (*Continued*)

Occupational characteristic	Dairy farmworkers (n=141)	
	No.	%
Type of PPE [g]		
Boots	84	59.6
Gloves	51	36.2
Aprons	23	16.3
Overall	4	2.8
Face masks	0	0.0
Previous job on dairy farms	15	10.6
Years with the job, Median (range)[h]	10 (1.5-17.0)	
Keeping livestock in their homes	0	0.0

[a] *The unmarried group only includes single dairy farmworkers, whereas the control group includes single, divorced & widowed.*
[b] *No other types were reported.*
[c] *Among smokers.*
[d] *Others include farm managers and security personnel.*
[e] *Rotating shifts involve 2 shifts in all workers (morning and evening /night shift), except parlor workers who work 3 shifts (morning, evening, and night shift).*
[f] *Including milking machines, loader trucks, tractors, and/or feeder mixers.*
[g] *Categories are not mutually exclusive.*
[h] *Among those who previously worked on dairy farms.*

one-quarter of dairy farmworkers used machinery at work (22.7%) and more than half used PPE (62.4%) with boots being the most frequently used form of PPE (59.6%) followed by gloves (36.2%), aprons (16.3%), and overall (2.8%). No dairy farmworkers reported wearing face masks. Only (10.6%) of dairy farmworkers had previously worked on dairy farms with a median working duration of 10 years. No dairy farmworkers kept livestock in their homes.

Table 2 summarizes symptoms. Throat irritation and/or sore throat was the most frequent respiratory symptom among dairy farmworkers (22.0%) followed by cough (19.9%), difficulty breathing (17.0%), and sputum production (15.6%) with higher overall respiratory symptoms than the control group (34.0% vs. 14.9%). Bronchitis was the most common respiratory disease among dairy farmworkers (10.6%), followed by allergic rhinitis and/or sinusitis (5.0%) and bronchial asthma (2.1%). Dairy farmworkers had a significantly higher prevalence of respiratory symptoms (throat irritation and/or sore throat, cough, sputum production, and difficulty breathing) than controls. Dairy farmworkers also had significantly higher rates of bronchitis and wheezes on chest auscultation compared to the control group.

Both measured, and percent predicted values of FEV1 and FEV1 /FVC ratio were significantly lower in the dairy farmworkers compared to the control group indicating an obstructive ventilatory change (Table 3). Regarding spirometry patterns, the normal pattern was the most frequent in both groups, with a significantly higher prevalence in the control group compared to the dairy farmworkers (90.6% vs. 78.2%, respectively). Obstructive patterns were significantly more common in dairy farmworkers than in the control group (19.4% vs. 3.1%, respectively) ($p \leq 0.001$).

The prevalence of obstructive spirometry patterns was highest among parlor workers (50.0%), followed by feeders and veterinary workers (16.7% for each) (Table 4). Restrictive ventilatory patterns were found in two workers: a feeder and a driver. Only one subject had a mixed spirometry pattern and was a parlor worker.

Bivariate analysis of dairy farmworkers' personal and occupational characteristics associated with abnormal spirometry patterns (Table 5) shows that

Table 2. Respiratory history and examination of the studied groups.

Respiratory variable	Dairy farmworkers n=141		Control group n=141		p-value
	No.	%	No.	%	
Respiratory symptoms [a]					
One or more symptoms	48	34.0	21	14.9	≤ 0.001
Runny nose, sneezing, and/or itching	6	4.3	4	2.8	0.520
Nasal congestion	15	10.6	7	5.0	0.076
Throat irritation and/or sore throat	31	22.0	14	9.9	0.006
Cough	28	19.9	14	9.9	0.019
Sputum production	22	15.6	11	7.8	0.042
Wheezes	5	3.5	4	2.8	1.000
Difficulty breathing	24	17.0	7	5.0	≤ 0.001
Respiratory diseases [a]					
Allergic rhinitis and/or sinusitis	7	5.0	2	1.4	0.173
Bronchial asthma	3	2.1	2	1.4	1.000
Bronchitis	15	10.6	6	4.3	0.041
Chest examination					
Wheezes	9	6.4	0	0.0	0.003

[a] *Self-reported.*

Table 3. Spirometry parameters and patterns of the studied groups.

Spirometry parameter	Dairy farmworkers [a] n=124		Control group [a] n=128		p
	Mean±SD		Mean±SD		
FVC [b]					
Measured (liters)	4.42±0.45		4.40±0.49		0.820
% predicted	95.37±11.39		94.73±11.57		0.657
FEV1 [c]					
Measured (liters)	3.44±0.66		3.63±0.46		0.008
% predicted	88.52±16.57		94.56±12.83		≤0.001
FEV1/FVC [d]					
Measured	77.43±11.44		82.57±5.99		≤0.001
% predicted	95.68±13.71		102.94±6.72		≤ 0.001
Spirometry pattern	**No.**	**%**	**No.**	**%**	**p**
Normal	97	78.2	116	90.6	0.007
Obstructive	24	19.4	4	3.1	0.001
Restrictive	2	1.6	6	4.7	0.282
Mixed	1	0.8	2	1.6	1.000

[a] *Seventeen of the 141 dairy farmworkers and 13 of the 141 in the control group declined spirometry.*
[b] *FVC: forced vital capacity.*
[c] *FEV1: forced expiratory volume in the first second.*
[d] *FEV1/FVC: the ratio of two volumes.*

Table 4. Frequency distribution of dairy farmworkers' abnormal spirometry patterns by job category.

Spirometry pattern	Obstructive (n=24)		Restrictive (n=2)		Mixed (n=1)	
Job category	No.	%	No.	%	No.	%
Parlor workers [a]	12	50.0	0	0.0	1	100.0
Feeders [b]	4	16.7	1	50.0	0	0.0
Veterinary workers [c]	4	16.7	0	0.0	0	0.0
Drivers [d]	3	12.5	1	50.0	0	0.0
Veterinary doctors [e]	0	0.0	0	0.0	0	0.0
Others [f]	1	4.2	0	0.0	0	0.0
p-value	0.509		0.266		0.880	

[a] *Parlor worker: mechanical milking of the dairy animals.*
[b] *Feeders: mixing, using feeder mixers, and distributing feed into different animal yards.*
[c] *Veterinary workers: breeding/caring for calves, as well as moving cattle from one location to another on the dairy farm.*
[d] *Drivers: using loader trucks and tractors to scrape, and remove manure from animal yards.*
[e] *Veterinary doctors: routine dairy animals medical care, such as examination, in vitro fertilization, and birthing, as well as vaccine and medication administration.*
[f] *Others include farm managers (administration and supervision), and security personnel (dairy farm guarding and general maintenance).*

dairy farmworkers with normal spirometry patterns and those with abnormal spirometry patterns differ significantly in age, smoking duration (years), working duration (years), and breaks during working shifts (P≤0.05), with these differences particularly evident among dairy farmworkers with obstructive ventilatory patterns. Significant risk factors from the bivariate analysis were entered into a binary forward stepwise logistic regression analysis to detect independent predictors of abnormal spirometry patterns. In the final model, older age (>37 years), longer smoking duration (>10 years), and longer working duration (>4 years) were independent predictors of abnormal spirometry patterns, particularly obstructive patterns, in dairy farmworkers after adjustment for breaks during working shifts.

4. Discussion

Occupational exposures remain an under-recognized and preventable cause of lung diseases, worldwide [30]. Dairy farmworkers are exposed to endotoxins and other potential respiratory risk factors, including gram-positive bacteria, molds, and fungi, as well as gases such as ammonia, methane, and hydrogen sulfide. The interactions between these agents are complex, and synergistic effects are likely. Clinical symptoms in exposed workers can range from asymptomatic sensitization, and rhinitis to bronchitis, and severe asthmatic attacks with impaired lung functions [14, 31].

In the present study, throat irritation and/or sore throat was the most frequent respiratory symptom among dairy farmworkers (22.0%) followed by cough (19.9%), difficulty breathing (17.0%), and sputum production (15.6%) with higher overall respiratory symptoms than controls (34.0% vs.14.9%), all of which were significantly more prevalent in dairy farmworkers than the control group [Table 2]. These findings are in keeping with a previous study conducted in Macedonia by Stoleski et al. [22] reporting that dairy farmers had a higher prevalence of work-related respiratory symptoms than office controls, being significant for overall symptoms (30.8% vs. 13.5%), cough (25.0% vs. 9.6%), and phlegm (15.4% vs. 3.8%). On contrary, these prevalences were higher than those reported by Eastman et al. [11] in a study of workers of large Californian dairies (>1000 lactating cattle per farm), in the United States where cough was the most frequently reported symptom (9.7%) followed by phlegm (8.1%), throat irritation (6.5%) and chest

Table 5. Association between dairy farmworkers' spirometry patterns and their personal and occupational characteristics.

Variable	pattern				p^f	COR (95%CI)	p^h	Pattern		p^g		p^h
	Normal (n=97)		Abnormal (n=27)				AOR (95%CI)[h]	Obstructive (n = 24)			COR (95%CI)	AOR (95% CI)[h]
	No.	%	No.	%				No.	%			
Age (years)												
< 37	68	70.1	3	11.1	**≤ 0.001**	Reference	**0.017**	2	8.3	**≤ 0.001**	Reference	**≤ 0.001**
≥ 37	29	29.9	24	88.9		18.7(5.2-67.2)	7.0 (1.7-173.6)	22	91.7		25.8(5.7-116.9)	23.1(2.0-264.6)
Residence												
Rural	80	82.5	21	77.8	0.579	Reference		18	75.0	0.396	Reference	
Urban	17	17.5	6	22.2		1.3(0.5-3.8)		6	25.0		1.6 (0.5-4.5)	
Current smoking habits												
Smoker	37	38.1	13	8.1	0.349	1.5(0.6-3.6)		12	50.0	0.289	1.6 (0.7-3.9)	
Nonsmoker [a]	60	61.9	14	1.9		Reference		12	50.0		Reference	
Duration of smoking (years) [b]												
<10	24	64.9	2	15.4	**0.002**	Reference	**0.038**	2	16.7	**0.004**	Reference	**≤ 0.001**
≥10	13	35.1	11	84.6		10.2(1.9-52.9)	3.8 (1.6-165.1)	10	83.3		9.2 (1.7-48.6)	11.9(1.1-150.4)
BMI (kg/m²)												
Obese [c]	5	5.2	2	7.4	0.646	1.5 (0.3-8.0)		2	8.3	0.624	1.6 (0.3-9.2)	
Non-obese	92	94.8	25	92.6		Reference		22	91.7		Reference	
Duration of work (years)												
< 4	57	58.8	2	7.4	**≤ 0.001**	Reference	**0.008**	2	8.3	**≤ 0.001**	Reference	**≤ 0.001**
≥ 4	40	41.2	25	92.6		7.8(4.0-79.5)	8.0 (2.7-840.0)	22	91.7		15.6 (3.5-70.4)	42.6(2.4-760.9)
Working hours/week												
< 72	62	63.9	22	81.5	0.084	Reference		19	79.2	0.155	Reference	
≥ 72	35	36.1	5	18.5		0.4 (0.1-1.2)		5	20.8		0.5 (0.2-1.3)	

Table 5. (*Continued*)

Variable	pattern				p[f]	COR (95%CI)	p[h]	Pattern		p[g]		p[h]
	Normal (n=97)		Abnormal (n=27)				AOR (95%CI)[h]	Obstructive (n = 24)			COR (95%CI)	AOR (95% CI)[h]
	No.	%	No.	%				No.	%			
Job category												
Parlor workers	32	33.0	13	8.1	0.371	3.2(0.4-28.6)		12	50.0	0.454	3.0 (0.3-26.6)	
Feeders	24	24.7	5	8.5		1.7(0.2-16.5)		4	16.7		1.3 (0.1-13.7)	
Veterinary workers	25	25.8	4	14.8		1.3(0.1-13.2)		4	16.7		1.3 (0.1-13.2)	
Drivers	6	6.2	4	4.8		5.3(0.5-60.8)		3	12.5		4.0 (0.3-48.6)	
Veterinary doctors	2	2.1	0	0.0				0	0.0			
Others [d]	8	8.2	1	3.7		Undefined[e] Reference		1	4.2		Undefined Reference	
Breaks during working shift												
Yes	70	72.2	14	1.9	**0.046**	Reference		12	50.0	**0.038**	Reference	
No	27	27.8	13	8.1		2.4 (1.03 -5.8)		12	50.0		2.6 (1.04-6.5)	
Previous job in dairy farms												
Yes	9	9.3	2	7.4	1.000	0.8 (0.2-3.8)		2	8.3	1.000	0.9 (0.2-4.4)	
No	88	90.7	25	92.6		Reference		22	91.7		Reference	

COR, crude odds ratio; CI, confidence interval; AOR, adjusted odds ratio.
[a] *Non-smokers and ex-smokers are both included in this group.*
[b] *Among smokers.*
[c] *BMI ≥30 kg/m^2.*
[d] *Others include farm managers and security personnel.*
[e] *Undefined as one of the studied cells in the 2 by 2 table is zero.*
[f] *Dairy farmworkers with normal spirometry patterns vs. dairy farmworkers with abnormal spirometry patterns (obstructive, restrictive, and mixed).*
[g] *Dairy farmworkers with normal spirometry patterns vs. dairy farmworkers with obstructive spirometry patterns.*
[h] *Variables with $P \le 0.05$ in bivariate analysis were considered significant (age, smoking duration (years), working duration (years), and breaks during working shifts) and were entered into binary forward stepwise logistic regression for prediction of abnormal spirometry patterns, particularly obstructive patterns, in dairy farmworkers.*

tightness (4.8%). The significantly higher prevalence of respiratory symptoms among dairy farmworkers in the present study may be attributable to their continuous and prolonged exposure to numerous respiratory hazards in the working environment including inorganic and organic dust, allergens, fungi, disinfectants (such as iodine, formaldehyde, and phenol, for the control of zoonotic diseases in dairy farms), smog-forming volatile organic compounds and gases emitted by cows and their wastes, such as hydrogen sulfide, methane, and ammonia. The combination of these exposures may result in respiratory irritation and inflammation.

The prevalence of bronchitis was significantly higher in dairy farmworkers than in controls in the present study (10.6% vs. 4.3%) [Table 2]. This finding corroborates the results of previous studies conducted in France [32, 33], and Norway [34]; all reported an increased risk of chronic bronchitis among dairy farming workers. Chest auscultation revealed a significantly higher prevalence of wheezes among dairy farmworkers than controls in the present study (Table 2). This finding is supported by the results of a study by Hoppin et al. [35] who demonstrated that interaction with animals increases the risk of developing wheezes (OR:1.26, 95%CI=1.08-1.48), and a dose-response relationship between wheezes and the frequency of milking *or* veterinary interactions.

In the present study, three out of 141 dairy farmworkers (2.1%) had bronchial asthma (Table 2). On contrary, a higher prevalence was reported by studies conducted in France (7.0%) [36] and the United States (5.0%) [12]. Additionally, the prevalence of bronchial asthma observed in the current study was lower than reported in a comparable study in Egypt among agriculture farmworkers (grape and strawberry farms) (7.3%) [19]. No significant difference in the prevalence of bronchial asthma was observed between dairy farmworkers and the control group in the present study, contradicting the results of Jenkins et al. [37] who reported that dairy farming in the United States was associated with a significantly increased risk of asthma ($p<0.001$; OR=1.542) and Eastman et al. [11], who reported that dairy workers had an OR of 2.73 for developing asthma compared to control workers. The finding in the present study may be attributable to the young age of dairy farmworkers (mean age, 35.8±10.7 years) and short working duration (median, 4 years). However, the development of bronchial asthma can be prolonged and is not often diagnosed as related to workplace exposure. Furthermore, dairy farmworkers accept respiratory symptoms as part of their jobs and do not seek medical help until symptoms become severe enough to preclude them from working.

Spirometry has long been used in occupational settings as part of medical surveillance to detect changes in lung functions [16]. The present study revealed that both measured, and percent predicted values of FEV1 and FEV1/FVC ratio were significantly lower in dairy farmworkers compared to controls; with a significantly higher prevalence ($p\leq0.001$) of obstructive patterns in dairy farmworkers than in the control group (19.4% vs. 3.1%, respectively) (Table 3). This was in concordance with a previous study conducted in France; in which cross-sectional and longitudinal analyses were performed in 1994 and 1999 in a cohort of dairy farmers demonstrated lower FEV1 in dairy farmers than in controls, with an accelerated decline in FEV1 / VC over time [32]. Thaon et al. [36] carried out a 12-year follow-up study on the same cohort to investigate lung function decline and found that dairy farmers had greater declines in FEV1 and FEV1 / FVC compared to controls. Further, Eduard et al. [34] reported that Norwegian livestock farmers had significantly reduced FEV1 compared to crop farmers. Eastman et al. [38] conducted a study on American farmworkers and reported that working in large California dairies was associated with mild acute airway obstruction, with both baseline and cross-shift reductions in FEV1 and FVC. In addition, Stoleski et al. [22] demonstrated a significantly lower FEV1/FVC % in Macedonian dairy farmers compared to office based workers.

On the other hand, a study comprising dairy farmworkers in the USA by Mitchell et al. [14] demonstrated a statistically significant association between working in large dairies and a cross-shift decrease in FVC. However, Nonnenmann et al. [12] found no association between working in dairy parlors and cross-shift measures of pulmonary health. The disparities in results may be attributable to a variety of factors, including differences in the demographics, and occupational characteristics of study participants, measures of occupational health and safety enforcement in the workplace, type of spirometry performed, and levels of exposure to respiratory hazards.

The reduction in the ventilatory functions observed among large herd dairy farmworkers in the current study may be due to proximity to aerosol sources (e.g. cattle), which contain a mixture of manure, animal dander, hair, animal feed, molecules derived from gram-positive and gram-negative bacteria (i.e. endotoxins), with large herd size (>1000 cattle). Moreover, prolonged duration of exposure in which the majority of dairy farmworkers with abnormal spirometry patterns had worked for four years or longer (92.6%), with nearly half not taking any breaks during their work shifts (48.1%). Further, no dairy farmworkers in the present study reported wearing face masks possibly due to a lack of awareness of the importance of wearing them. All these reasons could result in cumulative workplace exposure over time.

Older age (>37 years), longer smoking duration (>10 years), and longer working duration (>4 years) were independent predictors of abnormal spirometry patterns, particularly obstructive patterns, in dairy farm workers in the present study (Table 5). These findings are comparable to the previous studies conducted in France by Venier et al. [39] and Gainet et al. [33] who reported that older age and smoking were associated with accelerated declines in lung function parameters (VC and FEV1) among dairy farmers. A separate longitudinal study was conducted by Thaon et al. [36] to explore the influence of exposure to organic dust in French dairy and nondairy agricultural workers and reported that greater declines in FEV1 among all workers were associated with longer durations of exposure to animal feed handling and that current smoking was associated with accelerated declines in FEV1 and FEV1 /FVC. In addition, Arteaga et al. [2] conducted a study of dairy farmworkers in the United States and found that age-related decreases in lung functions were higher in dairy workers compared to controls ($p<0.001$), with FEV1 and FVC decreasing by 1 ml instead of 0.2 ml for every 10-year increase in age, and the number of consecutive days worked, was associated with decreases in FEV1. However, the aforementioned findings contradict a study conducted by Ahmed et al. [19] comprising 150 Egyptian agriculture farmworkers who reported lower age and duration of farming occupation were significantly associated with WRA. Our findings may be attributable to older workers being more likely to have a longer duration of exposure to hazardous substances, thereby increasing their susceptibility to declines in ventilatory functions. Furthermore, younger workers may find it easier to change jobs to avoid exposure [40].

5. Conclusions and recommendations

Large herd dairy farms, despite being open and naturally ventilated, are hazardous to the respiratory health of the workers and increase the risk of developing respiratory symptoms, bronchitis, and obstructive lung function changes. Accordingly, we strongly recommend the provision of PPE, particularly face masks and respirators, with proper training on appropriate usage, respiratory health screening using spirometry at baseline and periodically thereafter with more specific examinations, such as post-bronchodilation spirometry testing and plain chest radiography, smoking cessation programs, as well as mandatory breaks during working shifts and days off to allow time away from dust exposure. Future studies should focus on task-based dust inhalation exposure measurement and developing recommendations tailored to individual tasks.

Strengths: We believe this to be the first study conducted in Egypt focusing on the respiratory health of large herd dairy farmworkers.

Limitations: A proportion of participants declined spirometry due to fear of infection, even after explaining that all precautionary measures for conducting spirometry during the COVID-19 pandemic had been applied according to recommendations of Crimi et al. [29]. The reference values used to interpret spirometry results were based on age, sex, height, and ethnicity retrieved from the USA Population [27]. However, there are no current reference values specific to Egyptian populations. Due to a lack of funding and lack of devices due to unaffordability, measuring inhalable dust and bioaerosol concentrations in worker breathing zones was challenging.

Institutional Review Board Statement: The study protocol was approved by the Institutional Review Board (IRB), Faculty of Medicine, Mansoura University, (code number: MD.21.02.427).

Informed Consent Statement: Prior to the start of the study, informed written consent was obtained from both the farm owners and interviewees. Participants and farm owners were provided detailed information regarding the study including the title, objectives, and procedures, as well as assurances of participant data confidentiality and anonymity with data never to be used for purposes other than scientific research. Participation in the present study was completely voluntary, and study participants were free to withdraw at any time.

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Declaration of Interest: The authors declare that they have no conflicts of interest.

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A Descriptive Study of a Turkish Pneumoconiosis Case-Series

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Keywords: Pneumoconiosis; progressive massive fibrosis; occupational lung disease; sandblasters; ceramic workers; miners; dental technician; foundry workers; pulmonary tuberculosis

Abstract

Background: *The study aimed to examine the conditions and factors affecting pneumoconiosis cases to determine the dimensions of the pneumoconiosis problem.* **Methods:** *This retrospective study was conducted in a tertiary research hospital between January 1, 2014, and December 31, 2021. Five hundred ninety-seven patients with pneumoconiosis were included in the study.* **Results:** *Large opacities were detected in 157 cases. When we compared cases with and without Pulmonary Massive Fibrosis (PMF), age and concomitant pulmonary disease were higher in PMF cases, which also showed lower FEV1, FVC, and FEV1/FVC. PMF was more frequent in subjects with long dust exposure duration (more than 20 years) and concomitant pulmonary diseases, particularly tuberculosis. Three occupations, sandblasters, dental technicians, and ceramic workers, showed the earliest onset of pneumoconiosis.* **Conclusions:** *The study presents pneumoconiosis data in a mixed and large population and contributes to the implementation of evidence-based policies and interventions for countries like Turkey striving to cope with the problem of pneumoconiosis.*

1. Introduction

Occupational exposures remain an important cause of underdiagnosed and preventable lung diseases worldwide. As noted in a recent American Thoracic Society (ATS) report, workplace exposures contribute to the burden of chronic respiratory diseases, and there is an urgent need to improve clinical recognition of occupational lung diseases [1]. Introducing new products, such as artificial stones, if industrial hygiene controls are inadequate and enforcement of existing occupational health and safety standards is limited has added to the burden of occupational lung diseases [2]. According to the Global Burden of Disease Study, in 2017, the global prevalence of pneumoconiosis was approximately 527,500 cases, and 60,000 newly diagnosed pneumoconiosis cases were reported [3].

Pneumoconiosis is the lung's accumulation of inorganic dust and fibers that cause a fibrotic tissue reaction [4]. Prevention of the disease, which has no effective treatment, primarily depends on workplace exposure management and health management practices regulated within the relevant legal framework. Although pneumoconiosis is a well-known occupational disease in Turkey, published statistics do not reflect its burden. Occupational disease statistics in Turkey are assembled from insurance records and compensated cases, which prevents the observation of the entire picture of occupational

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lung diseases, rendering the at-risk population uncertain of preventive strategies and perpetuating the cycle of occupational exposure and disease unless the factors causing disease development are identified.

This study aimed to examine the conditions and factors affecting pneumoconiosis cases diagnosed in one of the important referral clinics in Turkey over the last eight years to determine the dimensions of the pneumoconiosis problem, the variables affecting disease development, and the necessary precautions and enable the development of recommendations.

2. Methods

2.1 Database and Study Population

This retrospective study was conducted at the Occupational Diseases Training Clinic of Ankara Atatürk Sanatorium Training and Research Hospital, an essential tertiary referral center for pneumoconiosis in Turkey. The ethics committee approved the study (2012-KAEK-15/2479). The study included all patients with pneumoconiosis admitted to the hospital between January 1, 2014, and December 31, 2021. An occupational history of inorganic dust exposure, radiological findings consistent with pneumoconiosis, and exclusion of other diagnoses established the diagnosis. All available examinations obtained while diagnosing pneumoconiosis during the study period were considered for analysis.

Experienced pulmonary and occupational medicine specialists took the medical histories and performed the physical examinations of all patients. Medical history comprises information on the present illness, past medical and surgical history, tobacco use history, family history, personal or social history, and comprehensive occupational history. The detailed occupational history documented the patients' present and past employment history and identified types of dust exposures at their workplaces. The occupational group was referred to as the job presumed to be the cause of pneumoconiosis by the occupational physicians of the clinic. We used the recorded smoking history to calculate tobacco pack years by multiplying the average number of cigarette packs per day by the total number of smoking years.

Spirometry was performed using the Zan 100 flow-sensitive spirometry device (ZAN Messgerate GmbH, Oberthulba, Germany). The spirometer was calibrated daily, with measurements of temperature and humidity used for calibration. The spirometry results were analyzed based on the acceptability and reproducibility criteria presented in the ATS/European Respiratory Society statement updating the standardization of spirometry. The patients' spirometry measurements were evaluated based on the percentage of the reference values.

Chest X-rays (CXRs) were taken with a digital X-Ray system. CXRs were evaluated by two readers separately and independently according to the International Labour Organization's (ILO) International Classification of Radiographs of Pneumoconioses, and the results were obtained in consensus. Small opacities are described by profusion, shape (rounded or irregular), and size. Small opacity profusion is classified into four categories (0, 1, 2, 3), each divided into three subcategories (0/- to 3/+). ILO profusion scores of 1/0 and above are considered pneumoconiosis. Progressive massive fibrosis (PMF) is defined as a large opacity exceeding 1 cm in diameter assigned to one of three categories according to the ILO International Classification of Radiographs of Pneumoconioses.

2.2 Statistical Analysis

The data of this study were evaluated using the IBM SPSS Statistics 22.0 statistical package program. Categorical data were presented as number (n) and percentage (%), and numerical data were presented as mean and standard deviation. Data were tested for normality with the Kolmogorov-Smirnov test. Kruskal-Wallis and Mann-Whitney U tests were used to analyze the difference in exposure duration between different radiological categories, and Spearman's correlation coefficient was used for correlation analysis. The Kruskal-Wallis test was also used to analyze differences in several parameters according to the occupational group, and the Mann-Whitney U test was used for *post-hoc* analyses. Large opacities and associated factors were evaluated with one-way analysis of variance, with the Tukey test used for post-hoc analyses. The relationship between the size of PMF lesions and pulmonary function tests was evaluated by Spearman correlation analysis. The chi-square test was used to compare categorical data. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Demographic Findings

This study included 597 patients with pneumoconiosis who had complete data in the analysis. Almost all patients were male (99.7%), and the mean patient age was 50.5±12.7 years at the time of diagnosis. Ever-smokers comprised 75.4% of the cases and had a median tobacco history of 22.8±15.5 pack-years. Existing pulmonary diseases were present in 231 (38.7%) cases; the most commonly reported diagnoses were chronic obstructive pulmonary disease (COPD; 27.5%), pulmonary tuberculosis (6.5%), and asthma (4.9%). Half of the patients were miners and foundry workers (n=302; 50.6%). The descriptive characteristics of the patients are shown in Table 1.

3.2. Radiologic and Pulmonary Function Test Results

When the CXRs of the pneumoconiosis cases were evaluated according to the ILO radiographic classification, the predominant small opacity was q (35.7%) and p (23.3%). When small opacities were

Table 1. Descriptive characteristics of 597 pneumoconiosis patients.

		Number (n)	Percentage (%)
Gender	Male/Female	595/2	99.7/0.3
Age (years)[#]	50.5±12.7		
Smoking Status	Current smoker	296	49.6
	Former smoker	154	25.8
	Never smoker	147	24.6
Smoking pack years (packs x years) [#]	22.8±15.5		
Occupation	Miner	158	26.5
	Foundry worker	144	24.1
	Welder	85	14.2
	Dental technician	49	8.2
	Stone worker	42	7.0
	Ceramic worker	39	6.5
	Construction worker	24	4.0
	Sandblaster	22	3.7
	Other*	34	5.7
Exposure duration (y, Mean & SD)	19.6±9.2		
Existing pulmonary disease	Chronic Obstructive Pulmonary Disease (COPD)	164	27.5
	Pulmonary tuberculosis	39	6.5
	Asthma	29	4.9
	Pulmonary embolism	17	2.8
	Sarcoidosis	10	1.7
	Lung cancer	8	1.3

**Glass workers, shipyard workers, brick factory workers, metal workers, tin workers, insulation workers, textile workers.*

grouped by size, small opacities between 1.5 mm and 3 mm were detected in 50.1% of the cases. Large opacities were detected in 157 cases, and 70 (44.6%) PMF cases were classified as category A opacities. The patients' radiological findings and respiratory function evaluations are presented in Table 2.

When the exposure duration to dust was compared to the dominant small opacity in patients with irregular dominant small opacities, it was longer than that of patients with rounded opacities (p=0.005). No statistically significant differences were found when comparing small opacity profusion score, small opacity size, and dust exposure duration. However, the mean dust exposure duration was slightly shorter in simple pneumoconiosis cases (p=0.053). There was no correlation between small opacity profusion score, dominant small opacity size, large opacity size, and dust exposure duration. When the relationship between dust exposure duration and spirometric findings was examined, while there was no statistically significant relationship between FEV1 and FVC values and dust exposure duration, FEV1/FVC was found to decrease as the dust exposure duration increased (r=-0.125, p=0.003).

Patients were classified as never smokers and ever smokers, and PFT results were analyzed according to large opacity size, small opacity size, small opacity profusion score, COPD, and pulmonary tuberculosis. Patients without large opacity were found to have higher average FEV1, FVC, and FEV1/FVC values in both smoking groups (ever-smokers and non-smokers) (p<0.001). In both smoking groups, patients with category C large opacities were found

Table 2. Radiological findings and respiratory function evaluations.

		Number (n)	Percentage (%)
Dominant Small Opacity	p	139	23.3
	q	213	35.7
	r	71	11.9
	s	87	14.6
	t	86	14.4
	u	1	0.2
Small Opacity by Size	<1.5 mm	226	37.9
	1.5-3 mm	299	50.1
	>3 mm	72	12.1
Small Opacity Profusion score	Stage 1	232	38.9
	Stage 2	256	42.9
	Stage 3	109	18.3
Large Opacity	None	440	73.7
	A	70	11.7
	B	43	7.2
	C	44	7.4
Pulmonary Function Testing*	FEV_1	77.8±20.5	
	FVC	80.6±18.7	
	FEV_1/FVC	77.9±11.9	

FEV1: Forced expiratory volume in one second.
FVC: Forced vital capacity.
** Presented as mean ± standard deviation.*

to have lower average FEV1, FVC, and FEV1/FVC values ($p<0.001$). When spirometric findings were compared by small opacity size, FEV1, FVC, and FEV1/FVC were lower as the opacity size increased in both groups ($p<0.05$). In addition, FEV1 and FEV1/FVC were lower in never-smokers and ever-smokers as the profusion score increased. In the latter group also, FVC was lower, increasing the profusion score. The FEV1, FVC, and FEV1/FVC values of patients with COPD were lower than those of subjects without COPD in both smoking groups. The FEV1, FEV1/FVC values of never-smokers with pulmonary tuberculosis and FEV1, FVC, and FEV1/FVC values of ever-smokers with pulmonary tuberculosis were lower than those of subjects without pulmonary tuberculosis ($p=0.029$, $p=0.010$, $p<0.001$, $p<0.001$, and $p=0.032$, respectively) (Table 3).

The size of large opacities was inversely correlated to FEV1, FVC, and FEV1/FVC ($r=-0.442$ and $p<0.001$, $r=-0.408$ and $p<0.001$, $r=-0.191$ and $p=0.019$, respectively). There was a negative correlation between dominant small opacity size and FEV1, FVC, and FEV1/FVC ($r=-0.388$ and $p<0.001$, $r=-0.353$ and $p<0.001$, $r=-0.226$ and $p<0.001$, respectively). FEV1, FVC, and FEV1/FVC were also inversely correlated with small opacity profusion score ($r=-0.312$ and $p<0.001$, $r=-0.316$ and $p<0.001$, $r=-0.147$ and $p<0.001$, respectively).

3.3. Comparison of Simple Pneumoconiosis and Pmf Cases

The age of patients with PMF was higher than that of those without PMF ($p<0.001$). FEV1, FVC, and FEV1/FVC were lower in PMF cases ($p<0.001$), and the PMF lesion size was inversely correlated with FEV1, FVC, and FEV1/FVC ($r=-0.442$ and $p<0.001$, $r=-0.408$ and $p<0.001$, $r=-0.191$ and $p=0.019$, respectively). PMF cases did not differ regarding smoking status, pack years, or average dust exposure duration. However, subjects with more than 20 years of exposure to dust were more frequently PMF cases than those with less than 20 years of exposure duration. ($p=0.010$). Concomitant pulmonary disease was detected in 70.7% of PMF cases compared to 27.3% in simple pneumoconiosis cases, constituting a statistically significant difference between the two groups ($p<0.001$). The prevalence of COPD was higher in PMF cases (55.4%) than in simple pneumoconiosis cases (17.5%; $p<0.001$). However, when COPD patients were analyzed according to smoking status, no significant association was found between smoking status and PMF. In addition, PMF was found frequently in patients with tuberculosis (69.2%) compared with those without (23.3%) ($p<0.001$). 64.7% of pulmonary embolism (PE) cases had PMF, while just 25.2% of those without PE had PMF ($p=0.001$). There was no statistically significant difference between PMF cases and those without asthma, sarcoidosis, or lung malignancy prevalence ($p=0.553$, $p=0.648$, and $p=0.125$, respectively; (Table 4).

3.4. Demographic, Occupational, Functional, and Radiological Findings by Occupation

In Table 5, we report the main study variables divided by occupation. Sandblasting workers were diagnosed at a younger age (36.8±6.6 years) compared to all other groups, whereas miners were diagnosed at a later age (61.3±12.3 years). Duration of exposure was found to be shorter in sandblasting workers (7.2±6.4 years) and ceramic workers (15.5±7.9 years). The prevalence of PMF was higher in ceramic workers (41.0%), sandblasting workers (40.9%), and dental technicians (40.8%). Welders (4.7%) had the lowest prevalence of PMF. Sandblasting workers (77.8%) had the highest rate of category C opacities, while there were no cases with category C opacities among welders.

Pulmonary diseases were found most frequently in sandblasting workers (72.7%) and least frequently in foundry workers (23.6%) and welders (24.7%). There was a statistically significant difference in the presence of pulmonary diseases among the occupational groups ($p<0.001$). The highest rate of COPD occurred in miners (41.8%); the highest rate of asthma occurred in sandblasting workers ($p=0.007$), which also showed the highest prevalence of tuberculosis ($p=0.004$) and PE ($p=0.007$).

The frequency of sarcoidosis and lung malignancy did not differ between occupational group.

Table 3. The relationship between pulmonary function test results and large opacity size, small opacity size, small opacity profusion score, COPD, and pulmonary tuberculosis existence according to smoking status.

	PFT results							
	Never smokers				Ever smokers			
Variables	**N**	**FEV1%**	**FVC%**	**FEV1/FVC**	**n**	**FEV1%**	**FVC%**	**FEV1/FVC**
Large opacities								
None	110	88 (77-96)	87 (78-96)	82 (78-87)	330	86 (73-95)	84 (74-94)	81 (75-85)
A	17	77 (61-84.5)	81 (72-86.5)	73.5 (65.5-77)	53	68 (58-82)	77 (63-89)	75 (62-79)
B	11	73 (58-93)	81 (54-92)	74 (69-79)	32	59 (55-78)	70.5 (59-83)	73.5 (60-83)
C	9	47 (34.5-60)	55.5 (49-74)	55.5 (50-78.5)	35	41 (31-58)	54 (42-67)	69 (60-74)
p#		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001
Small opacities								
< 1.5 mm	63	92 (79-101)	88 (81-98)	82 (78-85)	163	87 (78-96)	87 (80-97.5)	81 (75.5-86.5)
1.5-3.0	71	80 (65-90)	82 (72-90)	78 (73-84)	228	77 (64-91)	79 (66-93)	79 (71-84)
>3.0	13	67 (56-89)	78 (52-92)	77 (65-91)	59	57 (45.5-69)	63 (51.5-73)	71.5 (62.5-82)
p#		<0.001	0.004	0.024		<0.001	<0.001	<0.001
Small opacities profusion								
Stage 1	61	89 (77-101)	87 (76-98)	83 (78-87)	171	87 (75-95)	88 (79-96)	80 (73.5-85)
Stage 2	63	82 (65-94)	84 (72-91)	78 (69-82)	193	78.5 (64-92)	80 (65-93)	79 (71-84)
Stage 3	23	79.5 (72-89)	81 (72-89)	79 (76-87)	86	65 (50-77)	68 (56-80)	76 (68-82)
P#		0.020	0.128	0.001		<0.001	<0.001	0.006
COPD								
YES	31	58 (40-68)	66 (52-80)	69 (55-73)	133	58 (44-73)	68 (55-84)	67 (59-71)
NO	116	89 (80-96)	88 (81-96)	82 (78-86)	317	86 (75-96)	84 (75-94)	82 (78-86)
P*		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001
TB								
YES	12	67 (40-86)	77 (59-84)	69 (60-79)	27	57 (44-73)	62 (54-78)	75 (60-83)
NO	135	85 (73-95)	86 (76-94)	81 (76-86)	423	80 (66-93)	82 (70-93)	79 (72-84.5)
P*		0.029	0.067	0.010		<0.001	<0.001	0.032

All the results are expressed as median (IQR).
* *Kruskal-Wallis,* # *Mann-Whitney U Test.*

Table 4. Comparison of PMF and simple pneumoconiosis cases.

		PMF			
		Yes	**No**	**p**	**OR**
Age*, Mean+SD		55.8±13.2	48.6±11.7	**<0.001**	
Exposure duration (y)*, Mean+SD		20.7±9.8	19.3±9.0	0.053	
Exposure Duration	< 20 years, n (%)	76 (48.4)	266 (60.5)	**0.009**	**1.63 (1.13-2.35)**
	≥ 20 years, n (%)	81 (51.6)	174 (39.5)		
Smoking pack-years, Mean+SD		23.30±16.0	22.6±15.4	0.837	
Smoking habits, n (%)	Non-smoker	37 (23.6)	110 (25)	0.720	
	Current/Ever Smoker	120 (76.4)	330 (75)		
FEV_1 (%)*		61.5±20.8	83.6±17.0	**<0.001**	
FVC (%)*		69.2±19.6	84.6±16.7	**<0.001**	
FEV_1/FVC*		70.1±12.8	80.6±10.3	**<0.001**	
Pulmonary Disease#	Yes	111 (70.7)	120 (27.3)	**<0.001**	**6.44 (4.30-9.63)**
	No	46 (29.3)	320 (72.7)		
Pulmonary TBC#	Yes	27 (17.2)	12 (2.7)	**<0.001**	**7.41 (3.65-15.03)**
	No	130 (82.8)	428 (97.3)		
Pulmonary embolism#	Yes	11 (7)	6 (1.4)	**<0.001**	**5.45 (1.98-15.00)**
	No	146 (93)	434 (98.6)		
Lung cancer#	Yes	4 (2.5)	4 (0.9)	0.125	-
	No	153 (97.5)	436 (99.1)		
COPD#	Yes	87 (55.4)	77 (17.5)	**<0.001**	**5.86 (3.93-8.74)**
	No	70 (44.6)	363 (82.5)		

 # presents n (%) and chi-square was performed for statistical analyses.
** Mann-Whitney U test.*

4. Discussion

In this study, we have reported the detailed personal, occupational, laboratory, and radiological findings of a large pneumoconiosis cohort in Turkey to determine the factors that accelerate the development and increase the severity of pneumoconiosis in a mixed case group. The evaluation of patients working in different occupations known to cause pneumoconiosis sheds light on the occupational groups that should be prioritized when creating appropriate pneumoconiosis coping programs in countries like ours, which have failed to combat the problem of pneumoconiosis. Therefore, the most important endpoint of our study is the identification of sectors characterized by a high prevalence of pneumoconiosis. In our study population, the three occupations with the earliest onset of pneumoconiosis were sandblasters, dental technicians, and ceramic workers. In addition, the shortest dust exposure duration prior to the diagnosis of pneumoconiosis was noted in sandblasters and ceramic workers. In our study group, PMF was more common in ceramic, dental technicians, sandblasters, and stone workers than in other occupations.

An increased estimated relative risk of PMF was associated with longer dust exposure duration (more than 20 years) and with concomitant pulmonary diseases – particularly tuberculosis, pulmonary embolism, and COPD (unadjusted results). However, we found that smoking and small opacity profusion score were not associated with PMF presence. Several studies have reported on the importance of dust exposure intensity in the development of PMF

Table 5. Characteristics of study group according to occupations.

	Foundry Worker	Miners	Welders	Construction worker	Dental Technician	Ceramic Worker	Sand-blaster	Stone worker	Others	P
Age	47.5±9.8	61.3±12.3	46.9±8.6	50.3±11.9	43.3±11.5	44.2±9.2	36.8±6.6	49.8±10.2	49.4±13.2	**<0.001***
Exposure Duration (y)	18.4±8.1	19.8±7.7	24.3±9.4	23.2±11.4	21.1±9.0	15.5±7.9	7.2±6.4	21.2±9.0	19.6±12.0	**<0.001***
Smoking (pack-years)	22.0±16.0	25.9±16.5	20.2±11.0	28.4±21.7	19.3±13.3	18.6±13.8	18.3±10.9	24.0±15.2	23.8±18.0	0.089*
$FEV_{1\,(\%)}$	84.7±18.6	72.7±20.6	86.6±1.0	77.8±16.6	71.1±22.9	77.4±18.1	66.9±25.2	71.6±22.1	75.1±21.6	**<0.001***
FVC (%)	85.7±17.2	75.4±19.0	88.7±12.5	80.2±14.5	76.6±21.8	81.3±18.0	70.6±21.4	78.1±18.9	77.6±21.7	**<0.001***
FEV_1/FVC	80.8±11.8	74.9±12.8	80.4±8.7	76.4±9.7	77.8±10.1	77.5±10.0	77.0±13.9	74.7±15.3	79.2±11.7	**0.002***
Pulmonary Disease, n (%)	34 (23.6)	77 (48.7)	21 (24.7)	14 (58.3)	22 (44.9)	13 (33.3)	16 (72.7)	21 (50)	13 (38.2)	**<0.001#**
PMF	20 (13.9)	60 (38.0)	4 (4.7)	6 (25.0)	20 (40.8)	16 (41.0)	9 (40.9)	16 (38.1)	6 (17.6)	**<0.001**

[5-9]. In addition to high dust exposure, Ng et al. stated that PMF development was associated with a high score for small opacity profusion and concomitant tuberculosis, although it was not associated with smoking [9]. In a study by Maclaren et al., 1,902 miners were examined retrospectively: exposure to respirable dust, simple pneumoconiosis category, and age were associated with the development of PMF [10]. However, the relationship between the small opacity profusion category and PMF presence is controversial, as some authors have stated that relatively low small opacity profusion scores may lead to PMF due to the conglomeration of small nodules into large masses [11, 12].

Sandblasting often involves applying abrasive particles to a surface such as glass or metal with compressed air for cleaning or decorative purposes. Though the use of free silica in sandblasting activities is prohibited in most developed countries, unfortunately, no general legal regulations on sandblasting have been made in Turkey, except for its use in denim sandblasting. Cases of pneumoconiosis have been described in denim sandblasting workers, and this industry has caused a significant increase in silicosis cases and fatalities in the recent past in Turkey [13]. Bakan et al. reported a prevalence of PMF of 37.4% at the time of diagnosis and a 5-year survival rate of 69% in denim sandblasters [14]. Dramatically, a 4-year follow-up study showed an increased prevalence of pneumoconiosis in denim sandblasters from 55.4% to 95.9%, despite a cessation in dust exposure [15].

In our study, 22 (3.7%) cases were sandblasters; of them, seven worked in glass manufacturing, six worked in denim sandblasting, five worked in metal sandblasting, and four worked in Teflon pan manufacturing. Higher rates of PMF (40.9%) and concomitant pulmonary disease (72.7%) were found in sandblasters than in other occupations, consistent with previous studies [16]. Although the use of free silica in denim sandblasting in our country is well known, its utilization in Teflon-coated pan manufacturing is less studied. All cases in our study who performed sandblasting for Teflon-coated pan manufacturing had PMF lesions, and one case underwent lung transplantation. Our study results show that in order to prevent similar outcomes as those seen in denim sandblasting, it is necessary to be aware that employees in the Teflon sector are also at risk for pneumoconiosis. Lower age at the time of pneumoconiosis diagnosis and high incidence of PMF in freshly crushed silica making occupations may be explained by the piezoelectric properties of silica. [17-19]. Many *in vivo, in vitro,* and population-based studies have demonstrated how activities that produce electrostatically charged free silica, such as sandblasting, are catastrophic to the human lungs. Urgent regulations banning sandblasting activities that involve free silica should be put into effect.

The ceramic manufacturing process begins with the preparation of raw materials such as clay kaolin, quartz, and feldspar as well as auxiliary materials if needed. Silica- and silicate-containing particle exposure primarily occurs during raw material preparation and surface treatment and glazing procedures; however, pneumoconiosis has been reported in all steps [20-22]. In our study, we found early-age pneumoconiosis and a high PMF prevalence in ceramic workers, though we were not able to stratify the risk by work process, as most of the patients stated that they were involved in all components of ceramic production.

Numerous studies have evaluated the changes in lung function that occur with pneumoconiosis. Although it has been reported that obstructive, restrictive, and mixed respiratory function loss accompanies PMF, a detailed evaluation of the distribution of abnormal patterns by radiological category has not been fully documented. In this study, respiratory function findings were reported in detail. We demonstrated lower FEV1, FVC and FEV1/FVC values in both never and ever smokers' groups as the large opacity size and the small opacity size increased. Also we found and small opacity profusion score in both smoking groups. These findings indicate that both obstructive and restrictive pulmonary loss play a role in the pulmonary dysfunction caused by pneumoconiosis. In addition, although there was no statistically significant difference in smoking habit and cigarette pack-years between simple pneumoconiosis and PMF cases, the frequency of COPD in PMF cases was higher than in simple pneumoconiosis cases. Morgan et al. reported that PMF was associated with a significant decrease in FEV1 and

FEV1/FVC during the initial phase, but only minor changes were observed in FVC [23]. In the study by Yeoh et al., obstructive pulmonary function loss was reported in all categories of PMF; however, the prevalence of restrictive and mixed disorders became evident with the disease progression [24].

According to studies conducted in a variety of regions, an increased risk of pulmonary tuberculosis, ranging from 2.8- to 39-fold, accompanies pneumoconiosis [25-27]. Pulmonary tuberculosis causes structural damage that leads to pulmonary dysfunction and higher mortality rates in patients with pneumoconiosis. The National Tuberculosis Control Program has been successfully implemented in Turkey, and the incidence of tuberculosis has decreased from 29.4 per 100,000 in 2005 to 10.6 per 100,000 in 2020. However, the incidence of tuberculosis is not well known among patients with pneumoconiosis [28]. We found that the proportion of PMF cases with pulmonary tuberculosis was 6.5%, similar to the literature. Additionally, the proportion increased as the severity of pneumoconiosis increased. Patients with pneumoconiosis stage 2 and above had a 6-fold higher prevalence of tuberculosis than patients with stage 1, and patients with PMF had a 7-fold higher prevalence of tuberculosis than patients with simple pneumoconiosis. A limited number of studies have been conducted investigating the correlation between pulmonary tuberculosis and the clinical course of pneumoconiosis. In a 13-year observational study, 586 (4.6%) newly diagnosed pulmonary tuberculosis cases were in a cohort of 12,787 patients with pneumoconiosis [29].

This study has a number of strengths, including its setting at a referral center for pneumoconiosis evaluation, the mixed pneumoconiosis case group, and the detailed analysis of respiratory function according to pneumoconiosis severity. In addition, this study sheds light on occupations that have been little studied as causes of pneumoconiosis. This study also has several limitations. The study was conducted in the occupational diseases training clinic of a hospital required by law to report occupational diseases, and thus the characteristics of the participants may affect the results of the study. In our country, neither public authorities nor health service providers take sufficient interest in providing vocational rehabilitation after an occupational disease diagnosis, and adequate human and financial resources are not provided. In addition, after the diagnosis of pneumoconiosis, it is recommended that the person should cease working in pneumoconiosis-inducing jobs and terminate dust exposure. Therefore, the diagnosis of pneumoconiosis often causes employees to lose their jobs. For this reason, even if symptoms have developed, many employees are hesitant to seek health care services.

5. Conclusions

Understanding the prevalence, causes, and severity of pneumoconiosis is the foundation of prevention. When this information cannot be gathered through well-functioning occupational disease reporting systems, it becomes even more important to transform the data collected in occupational disease referral centers into scientific information. In conclusion, the current study presents pneumoconiosis data in a mixed and large population and contributes to the implementation of evidence-based policies and interventions for countries like Turkey that are striving to cope with the problem of pneumoconiosis. For future research, we recommend further exploration of the risks of occupations that have not been well studied but are identified in our study as having a high risk and the assessment of occupational disease prevention programs implemented in workplaces for pneumoconiosis eradication.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (2012-KAEK-15/2479, 03/08/2022).

Informed Consent Statement: Patient consent was waived due to retrospective design.

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Health-related Quality of Life and Determinants of the Mental Dimension Among Tunisian Nurses in Public Hospitals

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Keywords: Quality of life; mental health; public hospitals; nurses

Abstract

Background: *The objectives of this study are to evaluate the health-related quality of life (HRQOL) among nurses in Tunisian public hospitals and to identify the determinants of its mental dimension.* **Methods:** *A cross-sectional, bi-centric study was conducted within a representative sample of the 1,179 nurses assigned to 28 departments of two Tunisian public hospitals (n=301). A structured inquiry (socio-professional characteristics, occupational perceived workload) and validated questionnaires (Short-Form 12 Health Survey, Job Content Karasek's Questionnaire, Work Ability Index) have been completed. Statistical analysis was based on the* χ^2 *test for simple cross-tabulation, whereas multivariate analysis of correlations was based on multiple linear regression.* **Results:** *The response rate was equal to 97.34% (n=301). The mean age of nurses was 42.60±21 years, and nearly half of them (49.07%) had a poor mental quality of life. The multivariate analysis suggested an association between mental HRQOL and female gender (β=-.060), obesity and lack of regular physical activity (β=.0.89), musculoskeletal diseases (β=-.0.41), and poor ability to work (β=.387). This deterioration of the mental HRQOL dimension was also associated with job tenure (p=0.002), perceived workload (p=0.015), conflictual relationships with colleagues (β=.049), feeling of insecurity at work (β=.049), and the intention to leave the profession early (β=-.065).* **Conclusion:** *The results of this study showed that a considerable number of nurses had a poor mental quality of life. This study also identified factors associated with this deterioration. Acting on these determining factors may improve nurses' well-being and global health, as well as their work performance and the quality of care provided.*

1. Introduction

The health-related quality of life (HRQOL) is a multidimensional concept that has been increasingly investigated in the medical sciences and various disciplines [1-3]. It is difficult to assess the HRQOL given the broad range of definitions and the lack of a uniformly accepted and specific one [1-4].

Globally, HRQOL is a multidimensional concept that refers to a person's well-being in the areas of life likely to be affected by physical and psychological health status [4, 5]. Recent studies on nurses' HRQOL have concluded that it may closely affect the care quality, influence patient satisfaction, and affect the population's health at large [2, 4]. The mental dimension of this HRQOL may also

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increase the risk of error and endanger patient safety [7].

However, to the best of our knowledge, very few studies have focused on assessing HRQOL among this specific occupational category, in general, especially in northern African countries such as Tunisia [2]. The current study aims to evaluate the HRQOL among nurses in Tunisian public hospitals and identify its mental dimension determinants.

2. Methods

2.1. Study Subjects

A cross-sectional study was conducted with a representative sample of 1,179 nurses practicing in two of the largest public hospitals in central Tunisia. The sample size was calculated with Epi info software (version 06) according to the fixed level of accuracy for the results (n=301). The demographic and general characteristics of the study subjects are summarized in Table 1.

A sample was randomly drawn and matched according to age, gender, and work schedule. Nurses assigned to exclusively administrative tasks, and thus not directly involved in patients' care, were excluded. We also excluded nurses suffering from psychological or neuropsychiatric disorders, such as psychosis and neurodegenerative diseases, based on their occupational Medical records.

Thus, based on including and excluding criteria, the sample matching was based on the proportions of age, class, gender, and work schedule among the 882 performing nursing activities (Figure 1).

In the random sample of 301 nurses, the response rate was equal to 97.34%. The sex ratio (male/female) was 1.06 (men=51.53%), and the mean age (±SD) was 42.60±21years. Nurses aged 45 and over accounted for 53.92%. The mean nurse job tenure (±S.D) was 18.51±12.87 years [1-40 years].

Day workers accounted for 37.91% of nurses, constantly assigned to the night shift 15%, whereas 47.10% of nurses alternated day and night work. The always night work schedule was experienced by 71.33% of nurses during at least one month throughout their career, with mean duration (±SD) equal to 5.63±7.54 years.

Table 1. Sociodemographic, health and occupational characteristics of the sample.

Characteristics	
Sex ratio, male/female	1.06 (51.53%)
Age, years	42.60±2
Shift of work	
Nightshift	209 (71.3%)
Average duration, years	5.6±7.5
BMI*	
Average BMI, kg/m^2	26.5±3.5
Overweight	122 (41.6%)
Obese	61 (20.8%)
Workability index (WAI):	
Excellent or good	177 (60.4%)
Bad	116 (39.6%)
Perceived mental workload	
"Heavy"	133 (45.4%)
"Moderate"	135 (46.1%)
"Mild"	25 (8.5%)
Professional relationships	
Conflictual relationships with colleagues	181 (61.8%)
Conflictual relationships with superiors	166 (55.3%)
Job strain	58 (19.8%)

** Body Mass Index.*

The mean body mass index (BMI) was 26.51± 3.49 kg/m^2 [17.4-8.3 kg/m^2]. Among subjects, 41.64% were overweight, and 20.82% suffered from obesity without statistical difference between males and females.

2.2. Questionnaires and Data Collection

The Ethics Committee of the University Hospital Taher Sfar of Mahdia approved the study (P03-MT-2017). The inquiry form was completed during almost a half-hour individual and direct interview, the first part of which was dedicated to informing the participants of the study's objectives and collecting their informed consent.

The form investigates the HRQOL within the Short-Form 12 Health Survey, Version 1 (SF-12v1) [8, 9]. This generic HRQOL questionnaire was developed based on the long-Form 36

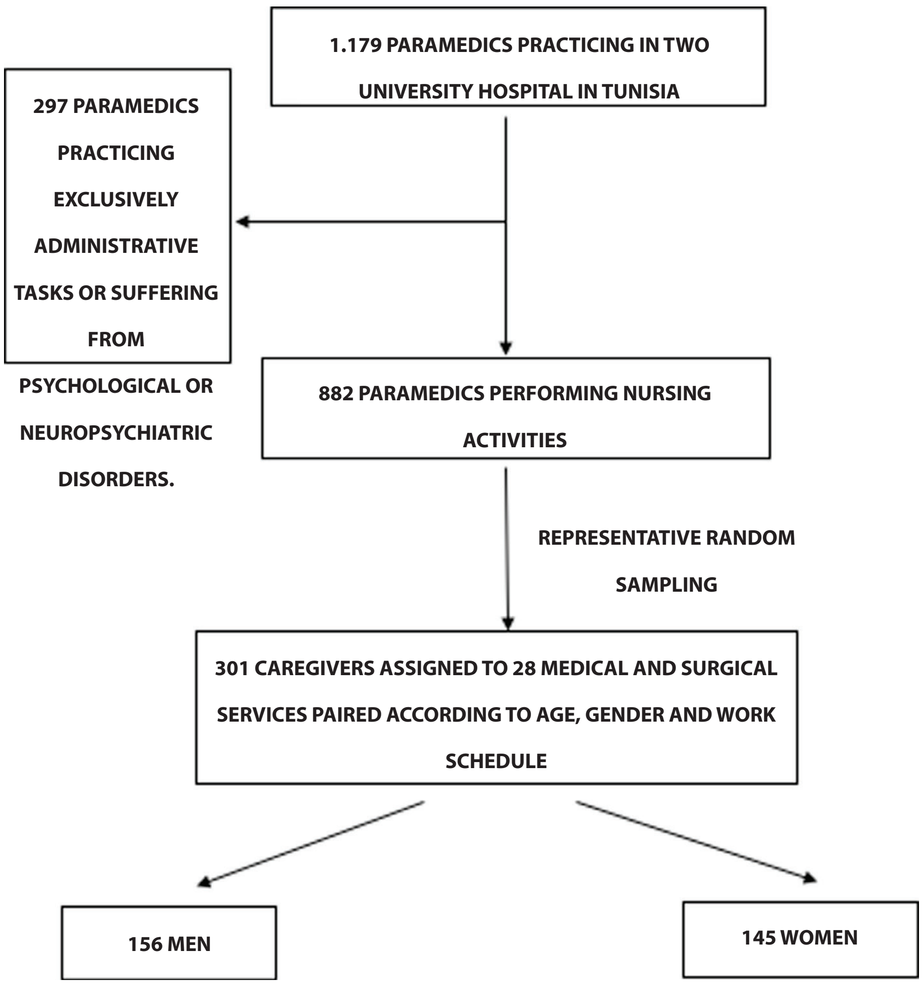

Figure 1. Study subjects: Flowchart of the random sampling.

Health Survey (SF-36). This shorter form (12 items) – like the standard version – calculates two scores: the Mental Component Score (MCS) and the Physical Component Score (PCS). These scores, obtained following the "original" scoring methods proposed by Ware et al., range from 0 to 100 [5]. A zero score indicates the lowest level of dimension measured by the scale, and 100 indicates the highest level of the measured dimension of HRQOL. The median score of the study population can be used to classify subjects' HRQOL [5, 7, 10].

This paper focused on the mental component score (MCS), which has shown good sensitivity (S.N.) and specificity (S.P.) [11]. According to the median MCS of the sample, two groups were identifiable: (i) the group of individuals with a poor mental quality of life, having a score lower than the median value of the population, and (ii) the group of individuals with a good mental quality of life with a score equal or higher than the median value of the population. The inquiry also investigated work constraints and work ability. Indeed, the perceived workload was assessed through a one-dimensional scale. This evaluation consisted in asking the operator to evaluate the workload associated with his / her current activity. Moreover, Karasek's Job Content Questionnaire (JCQ), a widely adopted questionnaire to assess psychological work-related factors, was used in its validated French version. This questionnaire was designed to evaluate psychological demands and decision latitude and to identify job strain situations defined by a ratio of job demands/decision latitude >1. Items assessing social support at work were combined to estimate better the psychosocial risks related to work [12, 13].

Work capacity was assessed by the validated French version of the work ability index (WAI). According to this seven-dimensional scale, work ability ranges from 7 to 49 and is classified as: poor, moderate, good, or excellent [13-15].

Nurses were also questioned about back and upper limb Musculo Skeletal Diseases (MSDs) symptoms', during the 12 months preceding the survey.

Moreover, there were additional questions associated with the inquiry form. These questions referred to the job tenure in the health sector, the feeling of uncertainty about continued employment (Job insecurity), and the desired retirement age and its reasons or motivations if nurses express any intention of early departure (before the legal age of retirement: 60 years).

2.3. Statistical Analysis

For data analysis, we calculated the means± standard deviations (S.D.), medians, and ranges of the quantitative variables. The χ^2 test was used for the comparison of two or more variables with statistical significance of Pearson coefficient set at <0.05

In order to investigate the association of HRQOL mental dimension with the sociodemographic, health, and work-related variables, multiple linear regression analysis was used. MSC was used as the dependent variable for the initial model, and a statistical thresholding set at 10% in simple cross-over was used to introduce variables. Analyses were conducted using SPSS statistical software (version 21.0).

3. Results

About one-third (31.68%) of nurses had at least one disease confirmed by a medical diagnosis. Over the12 month period preceding the survey, 69.62% of them reported Musculo Skeletal Diseases (MSDs) of the back, and 51.20% reported at least one upper limb MSDs.

3.1. Work Constraints and Ability

Among nurses, 119 (54.40%) described their perceived workload as "heavy", 135 (46.10%) felt it was "moderate" and only 25 of them (8.50%) found it "mild".

Moreover, according to the Karasek's questionnaire, 58 nurses (19.79%) were under Job strain. Among them, 39.9% mentioned the absence of support among colleagues and 44.7% among superiors. A feeling of job insecurity was reported by 73.72% of nurses. This feeling was more common among workers who reported a heavy perceived physical load (p=0.001) and those working regular night shifts (p=0.021).

The mean work ability index (WAI) was equal to 40±6.28 [21-49]. According to this index, 60.41% of the subjects felt that their work ability was excellent or good, and 39.59% considered it poor. Among nurses, the WAI decreases with age (p=0.005).

Moreover, 77.48% of nurses expressed the intention of early departure. The mean age of retirement desired was equal to 54.13±4.10 years. The main reasons for nurses' willingness to leave the profession were related to the high job strain and work conditions 34.5% and their health status 25.9%. This intention was more commonly expressed among young workers (age <45 years) ($p < 10^{-3}$) and female gender (54.18% women versus 45.82% men) (p=0.04).

3.2. Quality of Life Assessment and Its Determinants (Table 2)

According to the S.F. 12 scale, the mean component score of physical HRQOL (PCS) was 42.64±3.22 [17.96-63.62]. Nearly half of nurses (47.09%) had a low PCS. This latter deteriorated with age, the prevalence being lower among young workers than in older ones (p<0.001). The prevalence of PCS was lower among nurses with low back pain (p<0.001) and those having upper limbs MSDs (p<0.001). Besides, physical HRQOL deteriorated with a heavier perceived workload (p=0.031) and the intention of early departure (p=0.024).

The mean mental component score of HRQOL (MCS) was equal to 42.57±11.62 (14.83-71.64). Among nurses, 49.8% had a low MCS compared

Table 2. Multivariate analysis of determinants of mental quality of life.

Model	Non-standardized coefficients		Standardized coefficients	
	Beta S.E.		Beta	p
Female gender	-1.394	8	-.060	.010
Physical regular activity	1.570	7	.089	.027
Professional tenure <15 years	.207	1	.234	.002
Perceived physical load as light	-18	7	-.089	.015
MSDs back	-1.028	1	-.041	.000
MSD upper limb	-.274	4	-.039	.002
WAI	.716	5	.387	.000
Desire of premature leave	-.186	1	-.065	.007
Relationship with colleagues	.983		.049	.006
Job insecurity feeling	.629	7	.049	.034

*** Positive coefficient expresses a positive correlation between the variable and a better mental HRQOL(higher MCS).*

to the sample's median. During the last four weeks preceding the survey, 41.98% of nurses could not complete tasks at work as much as they would like to. During this period, 24.91% felt sad and down, while 83.28% felt confident about the future. Nurses perceiving their mental workload as "heavy" had a lower MCS without a statistical difference (p=0.06). However, the MCS was statistically lower among nurses with low physical component score HRQOL (PSC) (p=0.015). Moreover, the MCS was lower among nurses with back and upper limbs MSDs (p equal to 0.002 and <.001, respectively) and those expressing the intention to leave work in the healthcare sector prematurely (p=0.001).

In the final explanatory model of the multi-regression analysis, a better mental HRQOL dimension was related to:

- General characteristics of the individual (male gender, regular physical activity);
- Nurses' health status (the absence of upper limbs and back MSDs, the elevated WAI);
- Professional characteristics (low job tenure);
- Occupational constraints (good relationships with colleagues, absence work in safety feeling, low perceived workload, and the absence of intention to leave prematurely).

This model explains only 35% of the variations of the mental quality of life (R^2=0.35), with interesting model predictive capacities (meaning of variation of F <.001) and low collinearities between the explanatory variables (VIF indices <10).

4. Discussion

A bi-centric cross-sectional study was conducted to evaluate the HRQOL of Tunisian nurses working in public hospitals. This paper focused on mental HRQOL and its determinants. The response rate was higher than that in similar studies in the health care sector [1, 4, 16]. Several scales have been proposed to evaluate the quality of life as a global approach to the individual's health status [2, 17, 18]. The "Short Health Study Questionnaire", commonly known as The Short Form Health Survey derived from the "Medical Outcome Study", is one of the most widely used standardized tests [5, 9, 19]. The Mental Component Summary score of SF-12 (MCS) includes five items and has shown good performance in evaluating mental well-being and impairment related to mental problems [1, 5, 8, 11].

In the current study, the mean MSC score of the SF-12 questionnaire was 42.57±11.62 (14.83-71.64), with poor mental HRQOL noted among half of the surveyed nurses. This score was lower than that reported in 2014 in a sample of the general Tunisian population (n=3,582) and equal to 47.96 [9]. A survey conducted on 246 nurses who worked at Greece's public and private hospital units concluded a comparable MCS score (45.50±11.18) (20). Similar results were reported by Arslani et al., who concluded that poor mental HRQOL occurred among 41% of Iranian nursing staff (n=520) with the lower mental health of these nurses compared to the average of the general population of Iran [16].

According to the current results, the MSC score was correlated with individual and health characteristics and professional constraints. A literature review of papers published in English or Japanese between 1995 and 2012 and focusing on nurses' HRQOL and its predictors concluded eight categories of factors: personal characteristics, health behaviors, job-related personal characteristics, organizational characteristics, interpersonal relationships, perceived work environment, occupational stress and stress coping [21].

Gender was found to be the only demographic determinant of MCS in nurses. Indeed, lower mental HRQOL was noted among females compared to men. Several authors agree on the impact of gender on the quality of life. Many support that females have a lower mental dimension in the Qol [22-25]. Ruiz-Fernández et al. conducted a study with 1,521 nurses working in healthcare centers in eight Spanish provinces and observed a gender difference in mental HRQOL evaluated by SF12 questionnaires, with lower women's mean MSC scores compared to those of men [26]. Among the forwarded hypotheses, extra-professional burdens partly explain this deterioration (such as work-family conflict) [3, 22-25].

According to our results, advancing age was not a determinant factor of nurses' mental dimension Qol. In contrast, Oyama and Fukahori objectivated that ten studies selected in their literature review established that increased age was related to better mental health [21].

Moreover, in our study, nurses' MCS was statistically correlated with the physical dimension of HRQOL and some physical diseases and limitations. Indeed, the mean PCS score was 42.64±3.22, with a poor physical QoL noted among half of the nurses (50,9%) and a low self-assessment of their work ability among 39,59% of them. These latter issues were statistically correlated with the decrease in the MCS score of SF12.

Different authors have reported comparable results [3, 4, 27-29]. A recent study conducted among 585 nurses in Cypriot public hospitals with the SF-12 questionnaire concluded a positive linear relationship between the physical and the mental HRQOL dimensions (r=0.634, p=0.000) [3]. Underestimating one's ability to do their work effectively could affect their experience and mental QoL [27-29]. This theoretical approach could explain the decrease in the mental HRQOL dimension in the case of limited physical abilities.

Additionally, obesity was noted among 62.46% of the interviewed staff and was correlated with a decreased mental HRQOL. A cross-sectional online survey was conducted among the adult population in the USA that controlled for comorbidities and concluded that the physical and mental dimensions of HRQOL decrease with increasing BMI, particularly among women for mental HRQOL [30]. Obesity alters self-image, creates a sense of incapacity and underestimation of one's abilities and additional and increases stress which leads to a lower mental HRQOL, with even depression or compulsive behavior that could further increase weight [30-32]. In addition, our nurses' lack of regular physical activity was associated with a lower mental HRQOL. Several studies conducted among adults have demonstrated that being physically active is substantially linked to a positive impact on HRQOL, reflected by the promotion of mental and physical well-being. These studies suggest that individuals with a sedentary lifestyle and Physical inactivity pay less attention to their health, leading to a decrease in their HRQOL [33, 34]. However, several organizational factors have been reported as barriers to healthy eating and physical activity among nurses, such as changing and atypical schedules [35, 36].

According to these results, during the 12 months preceding the current survey, MSD symptoms of the upper limbs were noted among 51.20% of nurses, and back problems were reported by 69.62%. The analysis concluded a negative correlation between

MCS score and MSDs for upper limbs and back localization. Several studies have reported that nurses are at a higher risk of MSD, negatively impacting their physical and mental HRQOL [37, 38]. A recent study conducted among 2170 Chinese nurses reported a total prevalence of MSDs of 79.52%, with a significant decrease in both physical and mental dimensions of HRQOL among the affected nurses [38]. This relationship between MSDs and HRQOL may be explained by frustration and stress associated with functional limitations, particularly gestures required during care activity, and low levels of work motivation [37, 39].

Additionally, the mental dimension of the HRQOL was statistically more impaired among nurses with heavy workload perception, those reporting a feeling of job insecurity, those with a desire to leave the nursing sector prematurely, and those with conflicting professional relationships.

Heavy workload is commonly reported as one of the leading occupational stressors among nurses [40]. The perceived workload is associated with the nurse-patient ratio, inadequate resources, patient dependency, undone tasks, and planned activity interruptions [33, 40, 41]. The perception of heavy workload levels reduced efficiency and performance, limited nurses' job satisfaction, emotional exhaustion, and even burnout, in addition to a willingness to leave the nursing field prematurely and adverse patient outcomes and medication errors [2, 24, 42, 43].

In these series, lower mental HRQOL was associated with work insecurity, noted among 73.72% of questioned nurses, and the intention to leave the profession prematurely was expressed by 77.47 %. Recent research highlights the link between organizational issues, occupational job dissatisfaction, and nurses' intention to leave prematurely [24, 42, 44].

Organizational specificities of nurses' jobs are important predictors of stressful work environments [44, 45]. The stress experienced by nurses is mainly associated with conflictual relations between care team members, organizational factors such as role ambiguity, and unsocial working schedules [36, 42, 44]. Although findings observed in this study did not retain autonomy at work as a determinant factor of mental HRQOL, this correlation was reported by many authors [46]. The feeling of well-being associated with this autonomy allows freedom of planning and executing work, positively impacting the HRQOL [45, 46].

According to our results, nurses' conflictual relationships with superiors and colleagues negatively affected their mental HRQOL. Stress related to a conflicting psychosocial environment deteriorates work motivation, which is fundamental to facing activity demands, notably in highly psychological or emergency-demanding situations [41, 45, 46].

In total, our cross-sectional study was confronted with some limitations. One of the most critical limitations was the relatively small sample size. In addition, the variability of nurses' occupational characteristics, specifically regarding professional tenure. In conclusion, according to this study, the MCS score was impaired among nurses, and this impairment was more pronounced in women not practicing any regular physical activity, suffering from MSDs, or having unfavorable working conditions (characterized by a heavy workload, conflictual relationships, the feeling of insecurity or a desire to retire early). Priano et al., based on a literature review, concluded that healthy lifestyle behaviors, good physical activity and a healthy diet contribute to better HRQOL among nurses [47]. Furthermore, supplementary interventional research studies must be conducted to assess the impact of these factors on improving the well-being and global health of nurses, their work performance and quality of care provided, and patient security.

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The Gofman-Tamplin Cancer Risk Controversy and Its Impact on the Creation of BEIR I and the Acceptance of LNT

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Keywords: Linear non-threshold; cancer risk assessment; dose response; radiation; mutation; atomic bomb; nuclear power; EPA; fallout

Summary

The major public dispute between John Gofman and his colleague Arthur Tamplin and the United States (US) Atomic Energy Commission (AEC) at the end of the 1960s and during the early 1970s significantly impacted the course of cancer risk assessment in the US and worldwide. The challenging and provocative testimony of Gofman to the US Senate in early 1970 lead to the formation of the US National Academy of Sciences (NAS) Biological Effects of Ionizing Radiation (BEIR) I Committee in order to evaluate the accuracy of claims by Gofman and Tamplin that emissions from nuclear power plants would significantly increase the occurrence of genetic defects and cancers. BEIR I recommended the adoption of the linear non-threshold (LNT) dose response model for the assessment of cancer risks from radiation exposures. The US EPA adopted this recommendation and generalized it to incorporate chemical carcinogens, thereby affecting cancer risk assessments over the next decades. Despite the scientific limitations and ideological framework of their perspectives, Gofman and Tamplin are of considerable historical importance since they had essential roles in affecting the adoption of LNT by regulatory agencies.

1. Introduction

From 1969 through to the early 1970s, a major public dispute occurred between John Gofman and his colleague Arthur Tamplin and the United States (US) Atomic Energy Commission (AEC) that significantly impacted the course of cancer risk assessment in the US and worldwide. This paper shows that the provocative testimony of Gofman to the US Senate in early 1970 [1] spurred the creation of the US National Academy of Sciences (NAS) Biological Effects of Ionizing Radiation (BEIR) I Committee to determine the accuracy of claims by Gofman and Tamplin that nuclear emissions from power plants would cause widespread genetic defects and cancers. The actions of Gofman and Tamplin proved to be highly influential since BEIR I [2] recommended that the US Environmental Protection Agency (EPA) [which had replaced the Federal Radiation Council (FRC)] adopt the linear non-threshold (LNT) dose response model for the assessment of cancer risks from radiation exposures. The US EPA [3] accepted this recommendation and generalized it to include chemical carcinogens [4], thereby affecting cancer risk assessments to the present day. Despite their highly criticized analyses and strong ideological

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perspectives, Gofman and Tamplin proved to be of great historical significance because they played essential roles in catalyzing the adoption of LNT by regulatory agencies in the US and around the world and in preventing the worldwide expansion of nuclear power.

The process by which the EPA adopted LNT for cancer risk assessment is clearly rooted in the 1956 recommendation of the US NAS Biological Effects of Atomic Radiation (BEAR) I Genetics Panel [5] that reproductive and genetic risk assessments for ionizing radiation needed to switch from a threshold to an LNT dose-response model. However, how this recommendation affected the adoption of LNT by the EPA for cancer risk assessment is complicated and needs some clarification, especially since the report of the subsequent BEAR II Genetics Panel in 1960 [6] did not support the application of LNT for radiation-induced cancer risk assessment due to uncertainties in low-dose extrapolation [7]. The current paper explains how the adoption of LNT by the US EPA for cancer risk assessment occurred, discusses its scientific foundations, describes necessary precipitating events, and characterizes key personality traits that helped affect the switch from threshold to LNT. The story is an outgrowth of the Gofman and Tamplin controversy that dominated the debates on radiation risk assessment and on the adoption of nuclear power within the US circa 1970 [8].

Herein it is shown that the recommendations of the 1956 BEAR I Genetics Panel [5] on exposure limits for ionizing radiation were used by both the Federal Radiation Council (FRC) and the AEC to establish radiation emission standards (January 1, 1961) for the first series of nuclear power plants built in the US. Subsequently, Gofman[1] and Tamplin would challenge the public health foundations upon which these FRC and AEC radiation emission standards were based, claiming these standards yielded unacceptable risks of cancer and genetic diseases and needed to be tightened by at least a factor of 10. Their claims were based on the premise that the LNT dose-response model is valid and they occurred at a time when society greatly feared adverse health effects from radiation exposures. The widespread acceptance of LNT and the real fear of radiation combined to create serious controversy that eventually would end the expansion and development of nuclear power plants in the US. Ultimately, Gofman and Tamplin would have to leave Lawrence Livermore, an AEC entity, as it became for them a professionally inhospitable workplace. This paper will also show that the historically dominating influences of the NAS BEIR committees on LNT and cancer risk assessment for over 50 years had their origins in the controversies between the scientists Gofman and Tamplin and the FRC and AEC.

2. The FRC/AEC Create Nuclear Plant Emission Standards Based on BEAR I Genetics Panel Recommendations

In 1956 the BEAR I Genetics Panel [5] recommended that the contribution of man-made ionizing radiation to an individual not exceed 10 rem per reproductive generation of 30 years, with a focus on genetic-based reproductive endpoints. This recommendation assumed that exposure from medical and related uses were already accounting for about half of the 10 rem. Thus, they took the remaining 5 rem exposure value, and divided it by 30 years, obtaining a value of 0.17 rem/year for an acceptable level for population-based exposures. The BEAR I Genetics Panel asserted that there was no safe level of exposure to ionizing radiation and made estimates for genetic damage based on the LNT model. The Panel did not address cancer risk estimates.

At that time, the lowest absorbed dose of ionizing radiation that was believed to produce a statistically significant increase in cancer incidence from a medical or epidemiological viewpoint was $\geq$100 rem [11]. The natural background radiation for

1 - John Gofman had a Ph.D. in nuclear chemistry from the University of California at Berkeley (UCal/Berkeley) under the direction of Glenn Seaborg, who received the Nobel Prize for his discoveries of transuranium elements. Their combined efforts played a significant role in the development of the atomic bomb. After receiving his Ph.D., Gofman received an MD from the University of California at San Francisco. Gofman then became a professor at the UCal/Berkeley, doing significant research in the area of cardiovascular disease with a focus on HDL/LDL, receiving multiple highly prestigious awards. In 1963 Gofman accepted an offer from Seaborg, now director of the Atomic Energy Commission (AEC), to direct its radiation research and risk assessment program at the Lawrence Livermore Laboratory [9, 10].

most areas of the world is between 0.05 to 0.20 rad/year. Consequently, the 0.17 rem/year value became adopted by the US AEC for emission exposure standards for US nuclear power plants. The concern over approximately doubling background exposures was mitigated by the absence of evidence to show that living in high background radiation zones (> 0.75 rad/year) was medically harmful. Thus, the 0.17 rem/year value of the BEAR I Genetics Panel for genetic damage morphed into FRC guidance and AEC regulatory/legal emission standards that Gofman and Tamplin would then use to assess cancer risks.

No significant public dispute arose over the 0.17 rem/year emission standard when operations began on the first of several nuclear power plants. However, this situation changed markedly as disputes arose over emissions of the proposed Monticello nuclear plant, which was to be built about 35 miles northwest of Minneapolis, Minnesota [12]. These disputes would begin in 1966 when certain faculty at the University of Minnesota with public interest concerns demanded that the AEC provide answers to questions about the risks associated with exposures from ionizing radiation in drinking water. Although their concerns were somewhat parochial, this would change in 1968 when Dean Abrahamson, a University of Minnesota Professor, contacted his friend from graduate school, Donald Geesaman, who was working at the Lawrence Livermore Laboratory under the immediate supervision of Arthur Tamplin. Tamplin received his Ph.D. from UCal/Berkeley under the direction of John Gofman and was now working again under Gofman's supervision at Livermore, where they had both arrived in 1963. Their mission was to evaluate the environmental and public health concerns of radiation, which was an outgrowth of the AEC Plowshare Program/Atoms of Peace, an initiative of the previous Eisenhower administration. They were also evaluating the world-wide distribution and possible effects of radionuclides from above-ground testing and those inadvertently released to the environment from underground testing.

Abrahamson had gone to graduate school with Geesaman at the University of Nebraska and contacted him to ask for assistance in this effort to evaluate health concerns associated with the Monticello project. Geesaman shared the concerns of Abrahamson with Tamplin and Gofman, who initially did not consider the emissions from nuclear power plants to be a serious concern as, by comparison, they had been focusing on other potentially higher exposures. Nonetheless, Tamplin eventually became interested and convinced Gofman that a deeper consideration of the issue was needed [12].

During this period, the nuclear physicist Ernest Sternglass of the University of Pittsburgh published a highly provocative paper [13] claiming that above ground testing in the US over the past decades was responsible for about 400,000 infant deaths and two million fetal deaths. Sternglass received enormous publicity after being interviewed on numerous national media outlets and writing many popular spin-off and follow-up articles for the general press [14]. The Sternglass assertions became of great concern to the AEC, and Gofman was asked to evaluate them since he directed the AEC/Livermore radiation health assessment program. This evaluation was actually undertaken by Tamplin [15], who concluded that Sternglass had grossly overstated the potential harm by about a factor of ten for infant deaths. Tamplin was said to have become a "hero" at Livermore, as his paper had discredited the principal claims of Sternglass [10, 16]. However, Tamplin was not fully dismissive, claiming that premature infant deaths were likely, given an uncertainty range, with up to about 4,000 premature deaths possible. The AEC wanted Tamplin to publish the refutation of Sternglass in a genetics journal with a limited audience and not in a widely read journal, like the *Bulletin of Atomic Scientists* [10]. This suggestion was considered highly inappropriate by Gofman and Tamplin who then resisted this recommendation with a highly inflammatory response[2] that began what would become a major series of rapidly esca-

2 - Gofman [10] tells the story of how he had a discussion with two senior AEC officials on this matter, both (i.e., John Totter and Spofford English) whom he knew quite well. In fact, English had been a fellow graduate chemistry student with him at UCal/Berkeley. Gofman asserted they wanted to "white-wash" the findings and told them his opinions in offensive language. It is likely that his personal style contributed to both the publicity his opinions received as well as the hostility he would encounter at the AEC and elsewhere [17].

lating disputes with the AEC. The Tamplin [15] publication in the *Bulletin of Atomic Scientists* and their active engagement with the controversy over the Monticello emission standards redirected Gofman and Tamplin to the issue of low-dose radiation exposures and cancer risks. During the Monticello evaluation process, they became convinced that the dose response for radiation-induced cancer risk was linear, with no safe dose [10, 12, 16].

Gofman and Tamplin used their experiences with Monticello and the AEC nuclear power plant emissions to develop their version of cancer risk assessment[3]. During the summer and early fall of 1969, Gofman and Tamplin had finalized a manuscript on the topic. These efforts resulted in Gofman [11] making a plenary presentation to a conference at the Institute for Electrical and Electronic Engineers (IEEE) on October 29, 1969, in San Francisco[4]. It was at this time that Gofman and Tamplin made their case for LNT as it applies to low doses of ionizing radiation, thereby raising criticisms with the AEC emission standards for nuclear power plants.

In his presentation Gofman stated that:

> "… a hard look at what data do exist leads us to have grave concern over a burgeoning program for the use of nuclear power for electricity and for other purposes, with an allowable dose to the population at large of 0.17 rem of total body exposure to ionizing radiation per year. A valid scientific justification for this "allowable" dose has never been presented[5], other than the general indication that the risk to the population so exposed is believed to be small compared with the benefits to be derived from the orderly development of atomic energy for peaceful purposes."
>
> "… Unfortunately, all the hard data concerning dose-effect relationship in man are for total doses about 100 Rads. Our estimates, therefore, of the effect per rad are, to be conservative, based upon a linear extrapolation from high dosages down to very low dosages…"

Although Gofman and Tamplin did not identify the origin of the 0.17 rem/year value of the FRC/AEC, as noted earlier, it had its roots in the 1956 report of the BEAR I Genetics Panel.

Gofman and Tamplin then applied this value (0.17 rem/year) in a new way, that is, to use LNT to estimate the increase in cancer incidence. They did so by assuming there was a 1% increase in tumor incidence rate/year/rem (i.e., based on an assumed doubling dose (DD) of 100 rem) with this being built upon a natural cancer incidence in the US of approximately 280 people affected/100,000 people/year. When they applied this rate to 100,000 people over the 30-year period, the 0.17 rem exposure translated into 14 newly induced cancers/year. If everyone in the US were exposed to 0.17 rem/year from birth to 30 years, the total exposure greater than background would be 5 rem. Assuming that the risk for all forms of cancer plus leukemia is an increase of 1% in incidence rate/rem, this yields 5 x 1=5% increase in cancer incidence rate. Based on these calculations, Gofman and Tamplin estimated 14,000 additional cancers per year to the US population over 30 years of age. They next added 2,000 more cancers to the total after assuming enhanced

3 - Gofman's conversion to an LNT belief is not clearly presented in his writings. However, it is surprising that he does not highlight the influence of Hermann J. Muller and the perspectives of the radiation genetics community. Rather, Gofman appears to have been more affected by the epidemiological research on leukemia as reported in the late 1950s by Alice Stewart and Richard Doll and in the 1960s by Brian McMahon whose research he commonly cited. On December 18, 1969, Alice Stewart wrote to Gofman thanking him for his December 9th letter and articles and sharing new findings supporting a linear dose response.

4 - The invitation was arranged via an engineering colleague of Gofman's at Livermore [10].

5 - The NAS BEAR I Genetics Panel [5] had made mutation damage estimates and had addressed this question as it was based on 10 rem exposure. If Gofman and Tamplin had dug more deeply into this question, they would have learned that the most prestigious radiation geneticists in the country (i.e., BEAR I Genetics Panel) displayed profound uncertainties and very large differences between each other even when forced to accept LNT when making estimates. For example, panelist George Beadle (Nobel Prize recipient-1958) provided a range of damage uncertainty estimates from a low of 100,000 to a high of 200,000,000 mutational events from 10 rem. It was such extreme examples of uncertainty that created great concern within the BEAR I Genetics Panel. It would eventually lead them to deliberately hide their massive uncertainties and interindividual expert differences from the scientific community and the public [18]. If such uncertainties/differences were revealed, they felt that the public would be unable to consider their policy recommendations seriously. How this information would have affected Gofman and Tamplin is uncertain. However, they would have readily seen that even the expert radiation geneticists were confused, having little confidence in their estimates.

radiation susceptibility by young children, making the total increase to 16,000. Although the additional 2,000 cancer cases were without a biologically based numerical justification, some speculation was offered concerning the possibility of a much-accelerated DD for X-ray-induced cancers resulting from *in utero* exposures. However, this estimation of extra cancers was not added to the total due to the *in utero* exposures. The 16,000 cancer cases were soon morphed into 32,000/year when Gofman and Tamplin decided that the DD for radiation-induced cancer could be decreased in half (i.e., from 100 to 50 rads), thereby increasing the radiation-induced cancer potency by 2-fold[6]. The presentation of Gofman at the October 29th conference [11] generated no national media publications, only a modest article in a San Francisco paper [12]. However, this presentation was known to AEC leadership and raised concerns [10]. This situation would change in less than a month.

Before considering that change, it should be noted that Gofman and Tamplin misinterpreted the meaning of a DD when calculating their sensational estimate. It is easy to understand how someone might be confused by the term DD because that word pair obviously suggests that there is a doubling of any effect of interest when the DD of radiation is applied. However, that interpretation is incorrect for cancer incidence (a somatic effect in irradiated individuals). The term "doubling dose" was presented on page 25 of the BEAR I [19] Genetics Panel Report to the Public when discussing its attempt to estimate "tangible inherited defects" that are present in the first-generation following exposure of a human population to a "doubling dose" of radiation. Just as it would be for estimates of induced cancer in irradiated people, the text of the Panel's report shows that it would be incorrect to conclude that there is a doubling of "genetic effects" already in the first generation. The BEAR I [19] Genetics Panel assumed that the present level of genetic effects in 1956 was 2% in children in the population of the United States. That is, of 100,000,000 children, about 2,000,000 million would experience [harmful] effects of medical importance without any additional exposures to man-made radiation. The Panel's paragraph on this topic then stated: "If we [mankind] were subjected, generation after generation, to an additional DD of man-made radiation, then this present tragic figure of 2,000,000 would gradually increase by 2,000,000 more cases, up to an eventual new total of 4,000,000 [that being a new genetic equilibrium]. It would, to be sure, take a very long time to reach this equilibrium double value. Perhaps 10% of the increase, or 200,000 new instances of tangible inherited defects, would occur in the first generation." Note that this is for an exposure to the DD for many generations[7].

Gofman and Tamplin initially assumed a DD of 100 rem. The BEAR I [5, 19] report did not specifically recommend that value. The Panel did write [19]: "The lowest figure which has been responsibly brought forward for the DD is 5 r, and the largest estimates range up to 150 r or even higher. Recent work with mice (which are, after all, mammals)

6 - A decade after the Gofman and Tamplin [11] cancer risk estimates (1% cancer increase/year/rem) relating to emissions from nuclear power plants, leading groups such as the US BEIR Committee and other advisory groups reported cancer and genetic risk approximately 10-fold lower for the same exposure duration (i.e., 30 years). These estimates were also driven by an LNT model assessment but with a shallower slope [20].

7 - According to Sankaranarayanan and Wassom [21], the BEAR I Genetics Panel provided the first estimate of genetic risks over both the first and subsequent generations of offspring assuming similar exposures with each generation. The Panel developed an indirect method which was called the "doubling dose" approach, based on population equilibrium theory. The equilibrium theory is founded on the assumption that the stability of mutant gene frequencies within populations indicates a so-called balance between two opposing entities: spontaneous mutations (i.e., these occur and become part of the population gene pool at a given rate per generation and natural selection which eliminates the same mutation via early death/failure to reproduce). When the so-called "equilibrium population" is then exposed to radiation, more mutated genes enter the gene pool and are then the object of natural selection, with the population achieving a "new" equilibrium-between both mutation and selection. The duration (i.e., generations) to achieve the new equilibrium and the rate of occurrence are contingent on the duration of exposure, the genetic endpoint, induced mutations and the intensity of selection. The equilibrium theory was continued with the creation of BEIR I [2] but with the quantitative estimates modified by Russell's discovery of dose-rate, and refined to address various types of mutations such as autosomal dominant, sex-linked and multi-factorial diseases, providing estimates of the number of generations needed to achieve the theoretical equilibrium for each endpoint type.

gives some basis for thinking that the DD is not as high as 150 r. The experience in Japan gives some basis for thinking that the DD is larger than 5 r". Considering that the Panel otherwise ignored the massive study led by James Neel in Japan, this seems to be an almost insulting single use of his extensive data that revealed no apparent induced hereditary effects in the population exposed to atomic bombs [22]. Certainly, for the time, the value of the DD used by Gofman and Tamplin is reasonable even though their application of it makes no sense.

3. Background Assumptions of the Gofman and Tamplin Risk Estimation

On page 75 of the book *Poisoned Power* [23] Gofman and Tamplin provide a rationale for their radiation risk assessment methodology. They state that "countless geneticists have repeatedly cautioned society about the danger of allowing any increase in the rate at which any type of mutations is introduced into the general population". This statement is consistent with the recommendation of the BEAR I Genetics Panel [5] though not specifically cited in the book. Gofman and Tamplin [23] state that "geneticists know very well that background radiation induces mutations". They go on to cite a 1970 September 8 affidavit by Joshua Lederberg [24], a Nobel laureate, before the Public Service Board of Vermont. They claimed that Lederberg stated that the present FRC/AEC standard of 0.17 rem/year allows for a 10% increase in mutation rates. They then quote Lederberg who stated that the present standards should be more stringent being not more than about 1% of the spontaneous mutation rate. Lederberg then applied this concept to other environmental mutagens such as a host of chemical mutagens. Gofman and Tamplin [23] (page 80) then stated that "natural radiation probably accounts for about 5-10 percent of diseases and premature deaths due to genetic diseases. Since there were ~320,000 cancer plus leukemia deaths in the US annually as of 1970, Gofman and Tamplin assumed that background radiation would account for about 10% or 32,000 ([23] - pages 258, 260). This is the basis for how Gofman and Tamplin converted/forced their methodology to derive the 32,000 annual cancer cases, using the 1% increase in cancer incidence/year/rad, 4,000 more cancers from the very young and reducing the DD in half. They seemed to know the numerical target goal (i.e., 32,000 cases) and altered the model parameters to achieve this value.

It is important to note that the genetics community to whom Gofman and Tamplin refer was led by Hermann J. Muller and his radiation geneticist colleagues leading up to the BEAR I Genetics Panel recommendations for LNT in 1956. What Gofman and Tamplin omit is that Muller and Mott-Smith [25] addressed the issue of background radiation for mature spermatozoa in fruit flies. These are cells that lack most genetic repair processes. They determined that background radiation could account for no more than 1/1300th of the control group mutations in Muller's Nobel Prize winning research. That is, it would be nearly impossible to measure such a background dose treatment effect in such a biological model. While a case has been made for a higher background radiation mutation rate for humans due to their longer reproductive life, Gofman and Tamplin failed to cite the massive findings of James V. Neel that did not reveal a significant mutation effect in the offspring of atomic bomb survivors following 75,000 subjects with copious publications from the 1950s to the present [22]. Yet these findings received enormous publicity and were widely published in the peer reviewed literature by Neel and colleagues. Thus, the underlying functional assumptions of Gofman and Tamplin did not consider the Muller and Mott-Smith and Neel data. These data were contemporary to the research of Gofman and Tamplin, challenging the summary statements of the above cited "numerous geneticists". In addition, although Gofman and Tamplin cited the comments of Joshua Lederberg to support their case, they also failed to cite the written comments of Lederberg (October 16) [26] to the Pennsylvania State Senate. In these comments Lederberg stated that he did not support the Gofman and Tamplin cancer risk assessment on mechanistic grounds, concluding that their estimates were "highly implausible". This was also similar to comments by Marvin Schneiderman [27], a biostatistician for the US National Cancer Institute (NCI) and later a staff person for the NAS. He noted that the Gofman risk estimates were "too high by a factor of 10 even accepting all of his assumptions." These two individuals could not be construed as being agents of the AEC.

3.1. Gofman and Tamplin Risk Assessment Presentations

Gofman received an invitation to testify before the Sub-Committee on Air and Water Pollution, Committee on Public Works of the US Senate that was chaired by Edmund Muskie. The invitation had nothing to do with the October 29th IEEE presentation but resulted because he was an Associate Director of Livermore. However, Gofman's presentation on November 18, 1969, was not about Livermore practices but was an extension of the earlier IEEE conference presentation. The presentation to the Senate was entitled: *Federal Radiation Council Guidelines for Radiation Exposure of the Population at Large—Protection or Disaster?* Perhaps the strongest conclusion from this presentation was the following: "… we are speaking out in the strongest terms against the current guidelines for radiation exposure to the population at large. We are urging the Atomic Energy Commission itself to join us in seeking early downward revision of the Federal Radiation Council Guidelines". (page 674).

Gofman and Tamplin also stated: "The only sensible thing to do right now is to reduce drastically the Federal Radiation Council dose allowable to the population at large by least a factor of 10". (Page 666).

In contrast to the presentation in San Francisco, the Senate appearance generated considerable high-level national publicity, and even followed Gofman back to his job at Livermore. Although the Livermore leadership comments were not explicitly critical of what he had said, he was told that it would be necessary, in the future, to obtain clearance/approval of such presentations and related publications before they are given/published [10, 16]. AEC leadership claimed that they did not want to prevent him from doing his job but they did not want to be surprised. It would not be long until Gofman would test this statement.

Five weeks later, on December 28, 1969, Tamplin was scheduled to make a similar challenging presentation at the American Association for the Advancement of Science (AAAS) annual conference in Boston that had a special section on nuclear power [10]. Playing by the new AEC oversite rules, Gofman and Tamplin shared the proposed presentation material with the Livermore administration. To their great disappointment, there was much censoring of their proposed comments[8]. This infuriated Gofman and Tamplin and created heightened controversy and dispute. In the course of the dispute, Gofman claimed to have informed the key organizers at the AAAS that Livermore was a "scientific whorehouse and practices censorship… and anything coming out of the Livermore lab is not to be trusted" [9] and indicated that Tamplin would not give the presentation. With the emotions quite high over the issue of censorship, the Livermore administration backed down, permitting Tamplin to make his presentation without their influence and paying his travel to the meeting. However, the battle lines were drawn between Gofman and Tamplin and the AEC administration at Livermore and Washington, DC. The next confrontation would be about a month after the AAAS meeting. This time it was in Washington, DC, during the third week of January, 1970.

Gofman and Tamplin quickly concluded that they were facing a major confrontation with the AEC administration. However, Gofman may have felt to some extent protected since he could return to his professor position at UCal/Berkeley and perhaps also because his Ph.D. mentor, the Nobel Prize Recipient, Glenn Seaborg, was the director of the AEC, with political contacts in the White House. In addition, it was Seaborg who personally recruited Gofman for his AEC position in 1963. Based on Gofman's recounting of this period, it is not clear that he appreciated the pressure that he had put Seaborg under and how he was testing his former mentor and now director of his organization. Gofman decided that the new AEC strategy to stop his pro-LNT message was not going to be censorship, as they had apparently won that confrontation,

8 – The censoring action led to a volatile confrontation between Gofman and Michael May, a long time AEC administrator. According to Gofman [10], he told May exactly what he had conveyed to the AAAS personnel, with the same explicit language.

but would involve discrediting their message and scientifically embarrassing them. This would be attempted by bringing in multiple AEC-funded prestigious academic researchers who would also testify at the forthcoming Senate hearings. Gofman claimed that he had seen this strategy in action by the AEC over the past years with others. Thus, he anticipated a significant challenge and confrontation [10, 16].

So how did Gofman and Tamplin prepare for this major anticipated showdown in front of the Senate Committee on Atomic Energy? According to Gofman [10, 16], over the next three weeks he and Tamplin wrote 14 manuscripts on the topic of radiation, LNT, and cancer. Of these 14 manuscripts, there would be ten published in the proceedings of the Congressional hearings [28-37], ten would be specific to scientific topics (e.g., organ specific cancers, such as bone, breast, lung, etc., and other related topics) and a summary paper[9]. The other papers would be targeted for publications in different venues. Their strategy was therefore to be the aggressor, to take the challenge to the AEC via the use of the Congressional hearings. They adopted a strategy that was designed to take the AEC administration by surprise, and to hit the topic from so many angles, within a brief period of time, that it would not be possible for the AEC to be organized well enough to counter the Gofman and Tamplin offensive. In addition, since this was being carried out in the US Congress, Gofman and Tamplin were hoping to present an overwhelmingly convincing case that would compel the FRC and AEC to face political pressure and to drastically change their environmental and public health practices. Besides the strong focus on cancer risks, Gofman and Tamplin also estimated that the genetic effects in the population would produce a 5-50% increase of serious diseases and a quantitatively corresponding increase in the yearly death rate. This perspective contributed to their demand for a greater than ten-fold reduction in the radiation exposure standards.

As might be expected, the Gofman performance ramped up an already heightened controversy and the dispute became highly visible within and outside the government, affecting the media, the scientific community, the AEC, and the Livermore and Berkeley communities. Gofman and Tamplin were clearly viewed as "the enemy within," as Gofman would commonly characterize the situation [9]. These were two highly visible AEC scientists, with Gofman being a major leader who publicly challenged and embarrassed his organization and his former advisor. This would also lead to Gofman getting involved in major public debates with talented scientists from the AEC side (e.g., UCal/Berkeley Professor Thomas Budinger) with large attendances, all very formidable affairs, with huge implications [23, 38]. Gofman and Tamplin also became involved with litigation to remove from the federal government (i.e., AEC) the authority to regulate radiation emission standards for nuclear power plants. This case eventually advanced to the US Supreme Court where the Justices ruled against the legal arguments of Gofman and Tamplin. Besides lawsuits, Gofman and Tamplin pursued other publicly conspicuous spin-off activities that only exacerbated tensions between them and the AEC [12]. For example, in 1971 Gofman would help create and become the director of the Committee of Nuclear Responsibility (CNR) (Wikipedia), an activist group dedicated to stopping the threat of nuclear power. However, one of Gofman's activities was quietly overlooked but became influentially significant; it was the response of the US Senate to his Congressional testimony.

On January 28, 1970, only a week after Gofman's Senate testimony, Robert H. Finch, the Secretary of Health, Education and Welfare, sent a letter to

9 - Gofman [9] would state: "In about three weeks we wrote fourteen scientific papers. I'd never done anything like that in my life." The fact that they researched, assembled, drafted, revised and finalized 14 papers in about three weeks is nearly impossible to imagine, especially for those in the domain of scientific publication. The massively accelerated effort would affect the quality of the papers, the failure to properly assess the literature and to properly understand the complexity of each technical area. This made their efforts an easy target for experts in their respective fields. Ironically, it was this criticism that Gofman and Tamplin were trying to counter, yet their strategy actually enhanced it. A reflection of the limited scientific quality of their manuscripts supports the fact that little effort was made to publish these papers in peer reviewed scientific journals. The purpose of the effort was more political than scientific as Gofman and Tamplin understood that the issue would be decided at the highest political levels rather than in a drawn-out scientific process. Gofman and Tamplin's instincts and strategy would prove to be correct.

Senator Edmund S. Muskie with the following recommendation:

> "Drs. Gofman and Tamplin have raised the question of whether the present FRC guidelines are still acceptable. In the past ten years, since the formulation of the FRC basic guides, sufficient additional information has developed from epidemiological studies and animal[10] experiments so that revaluation of such guidelines is believed to be warranted.
>
> In view of our concern with the potential hazard of ionizing radiation in the environment, and as chairman of the FRC, I am recommending that the Council institute a careful review and evaluation of the relevant scientific information that has become available in the past decade. I am recommending that this reevaluation provide, as definitely as possible, estimates of the risk associated with low levels of environmental radiation as a basis for review of the adequacy of current FRC guidelines as applicable to projected radiation levels. Based on projected exposure classes of radiation sources, such as nuclear power reactors, other peaceful uses of nuclear energy, and radiation from consumer products would also be considered."

The FRC would soon contract with the NAS/ National Research Council (NRC) to establish the Advisory committee (i.e., BEIR I) to perform the type of review noted above by Finch. So acute was the controversy that, even before a study could get underway, Cyril Comar, Chair of the BEIR I committee, wrote to Charles Dunham, who had moved from the AEC to be head of the NAS Division, informing him that all leading radiation advisory organizations, domestic and international, are not in agreement with the Gofman and Tamplin analyses and recommendations [39]. However, Comar concluded that even though no evidence supported the Gofman and Tamplin position, "the allegations and widespread public concern generated by their actions has forced the committee to take up the issue as stated by Finch." [39].

4. The Gofman - Tamplin Affair in Perspective

The major conclusion of the present assessment is that this episode in environmental and public health history was an example of misguided scientific activism dressed in the garb of apparent high-powered science that patently failed to apply the gold standard for ensuring scientific quality: the process of peer review. In essence, stoking the public's fear of radiation with exaggerated claims of deadly diseases was used to influence the political process, instead of the scientific peer-review process, to accept an unproven (and possibly invalid) scientific model (LNT), thereby hindering the development and expansion of nuclear power plants in the US and around the world. In retrospect, the actions of Gofman and Tamplin were quite successful in ensuring that ionizing radiation would be viewed as acting without a threshold and, therefore, was the cause of, or significantly contributory to, a vast range of cancers and genetic related diseases.

It is hard to find two scientists who were more successful than Gofman and Tamplin in helping to achieve a major societal transformation. Their actions were highly significant in affecting the long-term cancer risk assessment policies of the US and many countries, and they did so without being a part of either the advisory committees that set these polices in motion or of the agencies involved in regulatory decision making. In fact, Gofman and Tamplin were a type of scientific/societal catalyst that activated a crucial step that was necessary to make the LNT policy changes occur. However, Gofman and Tamplin knew very well that, as AEC insiders, their professional careers within this organization were at great risk, not only because of their specific passionate opposition to the goals of their organization, but also because of the leadership style of Gofman. In the case of Gofman, he had a very generous and long-term funding arrangement at Livermore, without having to write competitive grants. He had an ideal arrangement for

10 - It has recently been discovered that William Russell, Oak Ridge National Laboratory, choose not to publish a large-scale animal study on lifespan and cancer risk involving a very large single (600 R) X-ray exposure to the male parent (~ 1959). No treatment related effects were observed. Russell would publish the findings some 35 years later in a coordinated effort to win a lawsuit in the UK [40]. It is not known how these findings may have impacted the low dose radiation risk assessment debate; however, it seems certain that it would have been used by the AEC to support their position and would have forced Gofman and others to address these findings. The Russell study was a very strong effort, even providing compelling evidence nearly 35 years later in the face of more stringent radiation standards.

a talented academic researcher. Yet, he risked and lost it in his principled quest to challenge the AEC to both rethink LNT and change its commitment to nuclear power. Although not as prominent as Gofman, Tamplin also put his career at the AEC in great jeopardy, and he was the first against whom AEC directed its professional emasculations. In the end, both men were compelled to leave the AEC, with Gofman eventually returning without his generous funding to UCal/Berkeley. According to Gofman [10, 16], his promised National Cancer Institute (NCI) follow-up funding also fell victim to AEC vindication. Gofman would take an early retirement and spend the rest of his professional life challenging the nuclear industry and strongly supporting the LNT model. Yet, despite his strong efforts to write modestly impactful books over the next three decades and to testify in multiple venues, Gofman had given up his academic base and had lost much power and influence.

Gofman may not have realized it, but he and Tamplin actually had won the major battle by instigating the NAS to create BEIR I and having NAS fill BEIR I members with many key supporters of Hermann Muller's LNT model (e.g., James Crow, William Russell, Edward B. Lewis). In 2021 the medical historian and colleague of Gofman, Henry Blackburn [41] wrote an insightful and sympathetic reflection on Gofman's life. In a follow up email communication by Blackburn [42] to the author (EJC), he revealed that Gofman lost everything in the process except his wits, but he still remained a positive and happy person. Many who would come to know the Gofman-Tamplin and AEC story would probably see them as courageous; this would also likely be the case for those having scientific and policy disagreements with Gofman and Tamplin.

Yet, within their truly courageous story, there is considerable and, at times, troubling complexity. The current assessment presents Gofman as knowingly venturing into a more-or-less "self-destructive" professional mission. To confuse and distract the AEC in the deployment of its professional resources against Gofman and Tamplin following Gofman's Congressional testimony, these men preemptively wrote 14 papers in three weeks on radiation cancer risk assessment that could be used to fully support Gofman's testimony and, thus, potentially ward off post-testimony criticisms from the AEC. This massive publication effort seemed even more daunting after the realization that Gofman and Tamplin had virtually no background experience in cancer risk assessment. Such a preemptive strategy signifies that Gofman and Tamplin were well aware of the AEC forces arrayed against them and also that the battle to be won was in the form of a political judgement rather than a scientific argument. Each of these 14 papers was designed to challenge leading authors, professionally and non-professionally, in key areas of cancer risk assessment. It is hard to comprehend the decision to undertake such a strategy, and yet the strategy ultimately managed to achieve its goal of sustaining the credibility of Gofman and Tamplin with key high-level elected officials, especially Senator Muskie. As expected, the Gofman testimony spurred presentations from leading experts in multiple areas of cancer risk assessment and radiation-induced mutations. In contrast to the sensational and personalized style of Gofman, the opposing perspectives were standard, hard-hitting professional rebuttals, avoiding personal attacks. It is generally recognized that many weaknesses and flaws in the analyses of Gofman and Tamplin were exposed during the rebuttals of the opposing scientists. However, whether the criticisms were accurate and on target was really not the overriding issue, especially since the scientific criticisms had been directed at a lay audience of elected officials and non-scientists. In fact, Gofman and Tamplin had won the debate by convincing the senators to create the BEIR I Committee very soon after the Gofman testimony. This "triumph" was glowingly underscored by Tamplin [39] soon after the publication of the NAS BEIR I Committee report in 1972. Tamplin [39] clearly had taken great satisfaction in their (Gofman and Tamplin) achievement, which was the endorsement of LNT by NAS BEIR I [2]. In the end, the BEIR I Committee was dominated by LNT-supporting committee members who readily endorsed the LNT recommendations of NAS BEAR I [5], but also decided to include a provision on cancer risk assessment. This decision would prove transformative within society as the LNT recommendations were soon generalized by EPA to encompass chemicals as well.

5. Summary Evaluation of the Gofman/ Tamplin Cancer Risk Assessment Approach

Given the above background, the next section briefly evaluates the analysis of Gofman and Tamplin [23, 43] that was used to challenge the emission standards of FRC/AEC. Their cancer risk assessment involved the leukemia data from the Japanese atomic bomb studies and the findings of Court-Brown and Doll [44, 45] for ankylosing spondylitis (AS), which involved leukemia and other cancers. Gofman and Tamplin followed the summaries provided by the International Commission for Radiation Protection (ICRP) [46] that were extensions of the 1957 report of Lewis [47], who made the first quantitative risk assessment for leukemia from these two populations.

The principal difference between the Lewis approach and that of Gofman and Tamplin was that Lewis also considered leukemia in two other populations (i.e., radiologists and children with enlarged thymuses that had been treated with X-rays to reduce their sizes) and did not consider other cancers; Gofman and Tamplin applied their cancer risk assessment to the FRC radiation emission guidelines that had been adopted by the AEC for nuclear power plants. The Lewis approach has been strongly criticized for each one of the four population groups he had evaluated [48, 49]. With respect to the AS, Gofman and Tamplin cited the 1965 paper of Court-Brown and Doll, which was an extension of their earlier findings (1957).

The study on AS and radiation-induced leukemia was a substantial effort funded by the British Medical Research Council. In the preface of the final published report [44] the Council wrote the following: "the present investigation was undertaken in the hope of obtaining an indication of the effects of small doses of radiation on human beings. From the nature of the case this could not be obtained directly, for few of the patients had received less than a mean dose of 250 r to the bone marrow; but it was hoped that a sufficiently precise relationship between the high doses of radiation studied and the corresponding increased incidence of leukemia could be derived to allow extrapolation to be made with reasonable confidence to lower levels of dosage. **"Unfortunately, this hope was not fully realized, for it is possible to derive more than one type of dose response relationship for the data," (emphasis added).** The authors of the report also stated to the Council in the preface of the report **"that until much more work has been done it will not be possible to decide between the alternative hypotheses." (emphasis added).** However, Lewis [47] failed to share this information with the reader while using the study to promote his goals.

The analysis of Gofman and Tamplin [23, 43] also failed to acknowledge the limitations expressed by the funding agency and by the researchers themselves. In addition, the dose to the spinal marrow used in the Gofman and Tamplin [23, 43] analysis was quite extreme, being 880 rad as the "average" dose. The disease estimation procedure involved a direct extrapolation from the 880 rad to the emissions standards of the FRC/AEC. The 1965 paper of Court-Brown and Doll did not disavow or modify their concerns and restrictions as clearly indicated in the 1957 paper. The principal value of the 1965 paper was the emergence of other cancers at what they called "heavily irradiated sites", a circumstance with the same very high to low dose extrapolative limitations. Yet, Gofman and Tamplin never mentioned these factors nor were they challenged to do so.

With respect to the Japanese survivor studies, the report of Gofman and Tamplin [23, 43] relied upon a summarized report that integrated an accumulating number of leukemia cases over time. Furthermore, there were several revisions concerning the exposure assessment to various types of radioactive agents in the cities of Hiroshima and Nagasaki by the Atomic Bomb Causality Commission (ABCC)/ Radiation Effects Research Foundation (RERF) as occurred in 1957, 1965, 1986 and 2002 [48].

Gofman and Tamplin [23, 43] simply adjusted their risk assessment calculation to be applied to the FRC guidelines based on cancer risk/year/rem assuming LNT. However, what they failed to do was to reconstruct an iterative dose response for leukemia cases throughout the 1950s and 1960s, as reported by Calabrese [48] who revealed a highly consistent J-shaped dose response throughout the 1950s, 1960s, 1970s, and 1980s, over a 40-year period. These estimates were based on following the original data, and each of the exposure reconstructions for each city (e.g., 1957, 1965 and 1986). These findings indicate that the linear dose response assumption of Gofman and Tamplin [11, 23, 43] was not supported. Thus, in the principal assessment that was directed to challenging the FRC guidelines, the core data and approaches used by Gofman and Tamplin were not supportive of their LNT hypothesis. These criticisms that challenged the LNT and the Gofman and Tamplin approach were provided in the 1970 Congressional Record, which contained the Gofman testimony/articles. However, the J-shaped response had been reported by Wald [50] and even discussed by the US NAS BEAR I Pathology Panel in 1956 [48, 51]; however, this group failed to pursue this viewpoint, probably because it did not conform to the existing paradigm, even though the J-shaped findings were a consistent feature of the data[11].

Gofman and Tamplin attempted to distract AEC experts and challenge their analyses by attacking published cancer dose-response studies for the radiation of multiple organs. One such criticism by Gofman and Tamplin [23, 43] was of radium studies conducted by MIT professor Robely Evans that supported the threshold model. This criticism led to a dispute with Evans over his sarcoma data. Evans indicated that his data were so dramatically non-linear that the linearity hypothesis displayed a statistical probability of less than 1 in 200,000,000 chance of occurring. Evans concluded that the odds against the linear assertions of Gofman and Tamplin were astronomical and not be even remotely supportable [54]. Gofman and Tamplin would also challenge the findings of William Russell that X-rays and gamma rays display a dose-rate effect in the male and female reproductive cells (i.e., stem-cell spermatogonia and primary oocytes), such that at low dose rates the damage is repaired. In the case of females, Russell [55] reported that it would take a dose-rate exposure some 27,000-fold greater than background before exceeding the repair capacity of the oocyte[12]. Russell claimed that there was a threshold dose-rate response in the primary oocytes but not in the stem-cell spermatogonia. It should be known that Russell [55] presented these findings at the May 5-7, 1969 conference at the Lawrence Livermore Laboratory that Gofman helped to direct.

Gofman and Tamplin [33] also provided their analysis of bone cancer in dog studies at the University of Utah to the Senate entitled: *Osteosarcoma Induction in the Beagle Dog with Alpha Emitting Radionuclides,* it was also submitted to the FRC a month later. Professor Charles Mays [56], who evaluated the Gofman and Tamplin paper, sent them a letter on March 25, 1970, concerning this paper:

> "… No doubt you wish for these organizations to be favorably impressed with the results of your calculations…
>
> Unfortunately, your manuscript contains a number of errors. For your convenience I enclose a copy with the numerical mistakes corrected in red for easy identification. This provides the opportunity to correct your manuscript before the official version of the Hearing is printed. Altogether, your 10 pages of text contains 71 numerical mistakes… However, errors of omissions of a much more serious nature exist… You have only selected those levels

11 - In 1981 Gofman [52] would finally address the issue of the J-shaped dose response for leukemia for both Hiroshima and Nagaski. His published analysis was not a strong one as it would cite only a single study of blood lymphocyte mutations as a biomarker for exposure that included only 18 people at Hiroshima whose exposures were beyond 2.4 Km from the hypocenter [53]. Gofman mistakenly claimed that there were 36 subjects from both cities. About half of the subjects reentered the city soon after the bombing, thereby receiving further exposures. No information was available on how this small sample was selected, their gender, occupation(s) and other relevant variables. Yet, Gofman would use this study to dispute the reliability of the massive efforts to reconstruct exposure estimates by the ABCC/RERF over the past thirty years in both cities. He claimed that the "control" subjects in both cities living furthest away from the hypocenter were exposed to about 6 rads more radiation than adjacent low dose exposure groups, thereby accounting for the J-shaped dose response for both cities. While the data were simply too limited and fragmentary for any conclusion, Gofman [52] used this study to reject the J-shaped dose response findings as being due to a low dose beneficial response or simply chance.

12 - In contrast to Bond, Evans and others who published written rebuttals to Gofman and Tamplin, William Russell presented a formal seminar at Oak Ridge National Laboratory in 1971 but published no follow up paper directed toward Gofman and Tamplin. According to Paul Selby (personal communication), then a graduate student of Russell, Russell gave his presentation to an audience that was much larger than normal. Selby indicated that Russell did not think very highly of the Gofman and Taplin assessment and exposed many flaws in their analysis.

> which happen to support your pre-conceived "law". You have disregarded those which do not. This is hardly likely to impress the scientific community nor anyone else for that matter. It is no new discovery that good fits to any line through data can be made by discarding the points which do not fit.
>
> In view of the importance of an accurate evaluation of the true cancer risk at low skeletal doses, and your biased selection of data, I am preparing a summary of all of our pertinent osteosarcoma induction results up to 1 April, 1970."

Months later (August 24, 1971) Mays wrote to the Senate stating that he had sent to Drs. Gofman and Tamplin their manuscript that contained the 71 errors and others of omission. He stated that: "It is with dismay I have learned that Drs. Tamplin and Gofman have not corrected their manuscript which related to our work, although they knew well in advance that their manuscript contained 71 numerical error (yes, seventy-one) and it deliberately omitted that part of our data which failed to support the linear hypothesis."

Gofman [57] would subsequently rebut some comments concerning the more trivial errors pointed out by Mays. However, Gofman was surprisingly unresponsive to the assertion that he and Tamplin disregarded data that did not fit with their LNT model.

Gofman [57] would also direct his rebuttal to comments of Victor Bond who provided a plethora of criticisms [58, 59] of the Gofman and Tamplin paper on breast cancer that was based entirely on the experimental research of Bond. Bond pointed out that Gofman only presented data on one study, ignoring data from other experimental studies and rodent strains in which radiation-induced mammary cancer risks were considerably less, and also cases where risks were less than control group (i.e., J-shaped dose response). That is, Gofman and Tamplin were very selective, using only data that supported their perspective, ignoring other non-supportive findings and not sharing their basis for such selection. Bond also pointed out that mammary tumors in the rats are not clinically relevant to human breast tumors, another point omitted/not addressed by Gofman and Tamplin. Of further relevance is that Bond [58] indicated that he estimated the annual risk from cancers in the US to be associated with the AEC exposure standards at 3,400 cases as an upper bound but with the risk being from zero to the upper bound with "the most probable value far below this figure" (i.e., 3,400). Gofman responded to this estimate in the following manner. He wrote that the AEC's Dr. Victor C. Bond's "conservative" cancer estimate for the FRC 170 millirad emission standard would yield "3,200 extra cancer deaths per year", with no mention of the Bond upper bound restrictions and related comments. Again, one finds that Gofman and Tamplin mischaracterized what Bond wrote, thereby giving a false representation. Furthermore, the reference that Gofman and Tamplin cited on page 107 listed the value at 3,200, not 3,400 cases per year. The "trivial" mistake of 3,200 vs 3,400 cases is also reminiscent of the Gofman and Tamplin papers being careless with details, as pointed out by Mays. This same issue is also seen in the 1981 book of Gofman [52] on the J-shaped leukemia data in which he did not provide easily obtainable information on several non-trivial critical study features that were materially relevant to the study.

6. The BEIR I Committee

When the NAS BEIR I Committee [2] assessed the effects of the atomic bomb explosions on the leukemia incidence of survivors, it relied upon papers that combined exposure groups in the 2.00-2.49 Km range with those at 2.50+ Km from the hypocenter into a single control group. These cumulative summaries of reported cases were established using the 1965 revised exposure assessment (i.e., TD65). By combining the lower dosed exposure groups, the respective papers indicated that the leukemia incidence at Hiroshima and Nagasaki was consistent with a linear dose-response model. In practical terms this meant that the "control" group included all subjects whose exposures were ~ < 5 rads [48]. The combining of the lower dosed groups in this manner was strongly criticized by Gofman [52] as being inappropriate for the data analysis, leading to incorrect associations in the critical low-dose zone. As noted above (see footnote 9), Gofman recognized the occurrence and consistency of the

J-shaped dose response of leukemia in Hiroshima and Nagasaki.

The present assessment indicated that the BEIR I Committee failed to properly assess the long series of cumulating radiation response data on leukemia. They settled for an LNT-biased analysis that grouped all data ~< 5 rad, thereby creating a biased analysis that assured an LNT conclusion. At the least, the BEIR I Committee should have acknowledged the occurrence of the J-shaped dose response for each city and attempted to account for these observations as did Gofman [52], and as was done later by Cuttler [60] and Calabrese [48]. The recognition of the failure of NAS BEIR I [2] to provide such an analysis is highly problematic from a scientific perspective.

7. BEAR I Geneticist Reflects on the Gofman - Tamplin Controversy

It is interesting to note that Sewall Wright, a member of the 1956 BEAR I Genetics Panel, wrote to William Russell on December 23, 1970, concerning the Gofman and Tamplin challenge to the FRC/AEC ionizing radiation emission standard. Wright [61] noted that: "They state that the evaluation of risk has been approached in the WORST possible fashion but it is not clear to me what they proposed unless it is a complete ban on all man-made radiation".

It is clear from the letter of Wright to Russell that the Gofman-Tamplin argument was in the far extreme and not consistent with current understanding of the role of genetics in human diseases, including cancer, leading to greatly exaggerated disease estimates. Similar concerns were raised by many others, as noted above, concerning Gofman during this time period. Nonetheless, in many respects, the positions of Gofman and Tamplin and Sternglass, seen in retrospect, appear to be like a negotiation in which opposing parties start with their highly polarized position. As noted earlier, Gofman and Tamplin were not successful in their attempt to eliminate the threshold-supporting authority of the AEC for nuclear power plant emissions, but they were successful in affecting the actions of elected officials, media, and the public concerning fear of all doses of ionizing radiation, no matter how small.

Wright further wrote that "They estimate that a dose of 5 additional rads up to age 30 would lead to a 5 to 50% increase in death rates (or 150,000 to 1,500,000 extra deaths per year in the U.S. population). They state that they derive this from the assumption that all human disease is due wholly to heredity, that the unfavorable heredity is due wholly to radiation, and that human beings would live forever but not this… Actually, heritability is not very great for most human diseases including cancer and mutations due to radiation are not the sole cause."

> "I find it difficult to reconcile their estimate of the damage of 5 r per generation… with the… relatively slight effects of 100's of r's... in your mouse colony."

8. Concerns with the Veracity of Gofman and Tamplin

On page 97 of the 1971 book *Poisoned Power,* Gofman and Tamplin [23] write that when they made their cancer estimates during the October 29, 1969, IEEE conference presentation, "we anticipated no opposition whatsoever to our scientific findings. We expected the nuclear electricity industry and the US AEC to welcome our report on the cancer plus leukemia, especially since the findings were being made before a massive burgeoning of the nuclear electricity industry. At that time (October, 1969), we had not given any special thought to the nuclear industry. In fact, in our preoccupation with a careful analysis of the hazard per unit of radiation received by the people we have thought the nuclear electricity as one of the most innocuous of the Atomic Energy programs, a view we have now had to alter radically." Thus, Gofman and Tamplin emphasized that at the end of October 1969 they had not given any "special" focus on the nuclear industry and radiation risks. The following information projects doubt on the veracity of this statement:

Gofman and Tamplin attended a conference at Livermore over March 5-7, 1969, on the "biological implications of the nuclear age". Tamplin presented a paper at the Conference that addressed human health risks of radioactive material from fallout. Gofman provided the conference summary.

Professor Dean Abrahamson from the University of Minnesota attended the conference and used it to meet Donald Geesaman, Arthur Tamplin and John Gofman. Abrahamson, Tamplin and Gofman participated in discussions on the radiation emission standard of 0.17 rem/year for nuclear power plants, the 0.5 rem exposure at the boundary of the facility, and the scientific foundations for these values. Thus, Gofman and Tamplin were aware by early March 1969 of the key issues and concerns of Abrahamson. What is also clear is that they learned that the 0.17 rem/year standard had been applied to genetic risk, not cancer. It would be in this application that Gofman and Tamplin would create much concern and attention. Of considerable importance is that Gofman and Tamplin did not acknowledge that the BEAR II Genetics [6] and Medical/Pathology [62] committees disavowed the use of linear extrapolation to estimate cancer risks from low-dose radiation exposures. Furthermore, Gofman and Tamplin actually forged ahead and practiced what the BEAR II (1960) Genetics and Medical/Pathology committees had explicitly recommended against, without ever citing that their approach contradicted BEAR II (1960) recommendations.

For the past several years before the 1969 conference at Livermore, Abrahamson challenged the AEC on issues related to its radiation emission standards and sought information and assistance from Geesaman and other key scientists at AEC (i.e., Gofman and Tamplin) who Geesaman recommended.

These four individuals (i.e., Abrahamson, Geesaman, Gofman and Tamplin) discussed public health issues related to the proposed Monticello nuclear power plant.

By summer of 1969, Gofman and Tamplin were convinced of the significance of radiation exposure issues raised by Abrahamson regarding the generation of electricity by nuclear power plants.

According to Semendeferi [12], Gofman and Tamplin had received at least two invitations by August 1969 to participate in meetings on nuclear power plants and public health issues related to emission standards for radiation exposures. One invitation for a meeting in September 1969[13] concerned the Rowe Yankee nuclear power plant in Vermont. The other meeting to be held on October 10 and 11, 1969, dealt with the Monticello nuclear power plant in Minnesota. These invitations were extended by Abrahamson.

The Vermont meeting: Gofman and Tamplin [43] wrote that "Tamplin went to Vermont with the sole purpose of trying to get the AEC to present an estimate of the biological effects of exposure at the FRC radiation protection guideline." The September 13, 1970 edition of the New York Times (page 35) [63] stated that: John Gofman also testified in Montplier, Vermont, and asserted that an additional 32,000 annual cancer cases could potentially occur due to nuclear power plants and that this estimate was very conservative. Semendeferi [12] stated that the AEC experienced its first public setback for generating electricity from nuclear power at that meeting. This was principally due to the actions of Tamplin and Gofman who publicly tried to compel the AEC to provide numerical estimates of health risks from exposure to radiation at the FRC emission guidelines. Semendeferi [12] also stated that at the Vermont meeting the AEC stigmatized Gofman and Tamplin as critics of the nuclear power industry.

The Minnesota meeting: Harry Foreman, who organized the Minnesota symposium, sent an invitation to Tamplin on August 4, 1969. In the letter he stated "The atmosphere in Minnesota is highly charged vis-a vis nuclear energy and doubts by reputable scientists (such as yourself) may well result in a furor that could drive nuclear power plants from the state forever…". According to Gofman and Tamplin [43] Tamplin formally argued at the Minnesota meeting that "the guideline dosage for exposure of the population was inappropriately too high and that no one should consider exposing the population to anything close to the guideline dosage."

According to Semendeferi [12] (page 80), the participation of Gofman and Tamplin in the nuclear power issue markedly strengthened the position of the Monticello opposition. Local newspapers highlighted the views of Gofman and Tamplin with

13 - The Rowe Yankee nuclear power plant in Vermont was the first major facility in the US, starting operations in 1961.

respect to the Monticello dispute. Tamplin [64] published an article based on his presentation at the Minnesota meeting in which he proposed to apply their risk assessment methodology to the effluents of nuclear power plants. He concluded his paper stating that "I view the burgeoning nuclear power industry with a great deal of anxiety. My impression is that these power plants should be designed so as to approach absolute containment of radioactivity."

Documentation of the actions of Gofman and Tamplin from early March to mid-October, 1969, contradicts their statements in the book *Poisoned Power*. That is, before the October 29, 1969 IEEE conference, Gofman and Tamplin claimed they had not given special thought to the possibility of nuclear power plants exposing the public to harmful levels of radiation. However, this claim of Gofman and Tamplin is contradicted by their documented involvements prior to October 29, 1969, in preparing, traveling, and participating in meetings on radiation exposures from nuclear power plants as well as in their pre-October written and spoken critiques of the AEC. Furthermore, Gofman's IEEE presentation was framed around the nuclear power plant emission standards that Abrahamson had already introduced to him well in advance of the October 29, 1969, meeting. This documentation indicates that the presentation at the IEEE conference had been significantly affected by prior considerations of issues related to health concerns with emissions from nuclear power plants. These claims of Gofman and Tamplin in *Poisoned Power* were incorrect and dishonest. Perhaps they were trying to create the image of an honest broker with no stake in the game since concealing their previous involvements and positions on radiation emissions from nuclear power plants, as they did in *Poisoned Power*, would seem to help foster their "honest broker image". In my opinion, the multiplicity of events and the close timing of the writing of the book to the actual events makes a convincing case that Gofman and Tamplin were deceitful. Other actions by Gofman and Tamplin also displayed a pattern of deliberate deception and manipulation, such as misrepresenting the findings of Bond, Evans, Mays and others in Congressional testimony while, at the same time, failing to share and/or explore contravening evidence such as the massive mutational data of Neel on the children of Japanese survivors of atomic bombs [22] and the issue of background mutations addressed by Muller and Mott-Smith [25].

9. The Enabling of Gofman and Tamplin - It Started with BEAR I Deceptions

The political success of Gofman and Tamplin within the Senate and joint Congressional committees of the US Congress was significantly affected by prior activities of the radiation genetics community. The most significant scientific aspect was the leadership of the US NAS BEAR I Genetics Panel that recommended a switch from a threshold to a linear dose response model in 1956 for radiation-induced genetic risks. This occurred amid enormous positive and unchallenged publicity. What the public did not know from the BEAR I Genetics Panel reports and publicity was that the panel deliberately misrepresented the scientific record concerning the extent of professional uncertainty and variation amongst the geneticists concerning risks from radiation-induced mutation [65]. The public/scientific communities did not know that the panel removed the three most divergent estimates of panel members to give the impression of conformity and agreement amongst the remaining six estimates (now hidden from the scientific community) and that the range of uncertainty among the remaining six was much more extreme than the panel reported. The public/scientific communities also did not know that another three members refused to even provide estimates based on the vast uncertainties. On page 146 of the Gofman and Tamplin [43] book '*Population Control' through Nuclear Pollution*, Tamplin states: "The question is not with your ability to detect [illness/disease], if indeed it cannot be detected, it is what is the numerical value, theoretically. Obviously, if you cannot detect it, there is no other way you can arrive at it. If the present levels of radiation protection guidelines have been set,…..by a group of competent scientific individuals who have weighed this situation carefully, then that must mean that they have an idea of what the precise effect would be, theoretically at least, on a scientific basis." One sees here that Gofman and Tamplin would rely on the authority of groups like the BEAR I Genetics Panel to provide the country with the best scientific understandings. What Tamplin did not know was that the BEAR I Genetics Panel committed scientific misconduct, hiding their uncertainties and misrepresenting the scientific record [65, 66].

This same panel also refused to give standing to the 10-year atomic bomb offspring mutation study of James V. Neel, who himself was a panel member, explicitly because the findings did not show a treatment related effect. Neel would eventually challenge Hermann Muller on this matter, but only after the major NAS BEAR I [5] Genetics Panel reports were released to the public [22].

During this period of Panel meetings, William Russell, another BEAR I Genetics Panel member, completed a large longevity and cancer study with mice that showed no treatment effect in the offspring of highly exposed males (see footnote 8). Almost certainly because of the negative findings, Russell deliberately hid these results from the scientific community, failing to submit the research for publication and keeping it secret from major advisory committees, some of which he was a member. Russell would eventually publish this research some 35 years later to help win a major lawsuit in the United Kingdom [40].

In 1960 the BEAR II Genetics Panel released two reports, a technical [6] and public summary [67], updating their 1956 publications. In this updated reporting, the technical report of the Panel indicated that it was inappropriate to estimate cancer risks at low doses/dose rates due to unacceptable uncertainties in the extrapolation process. However, this most critical statement was omitted from the public report. Yet, it is hard to imagine a more significant conclusion, and it being one not shared with the public.

A detailed evaluation of the LNT cancer risk assessment methodology used by Gofman and Tamplin reveals that they assumed that the LNT dose-response model developed specifically for assessing risk of radiation-induced genetic mutations could also be used for assessing risk of radiation-induced cancers. In other words, without experimental proof, they assumed that the two biological processes of mutagenesis and oncogenesis were essentially equivalent and that the LNT model could be used interchangeably to predict mutagenic and oncogenic risks. However, the mechanistic processes of mutagenesis and oncogenesis have been known to be vastly different and complex processes for quite some time by many prominent scientists. In fact, the BEAR II Genetics and Medical/Pathology Panels may have also thought so at the time as they strongly rejected use of the LNT dose-response model for cancer risk assessment. If Gofman and Tamplin knew that the BEAR II 1960 Genetics panel [6] explicitly rejected the use of LNT for a low dose cancer risk assessment, they should have been honorably obligated to acknowledge it and explain their rationale for using it. However, since this did not happen, Gofman and Tamplin either knowingly ignored the BEAR II rejection of LNT in cases of cancer risk assessments or were completely ignorant (unaware) of the BEAR II rejection. Since knowingly ignoring it without explanation would be considered a dishonorable act and ignorance of it would imply incompetence, neither action could be considered acceptable or laudable behavior for prominent scientists such as Gofman and Tamplin. In any case, the end result was that Gofman and Tamplin used LNT to make predictions of cancer risks that stoked public fears and convinced anxious senators to legislate a legacy of LNT-biased BIER committees, perpetuating LNT ideology.

Furthermore, Gofman and Tamplin calculated that background radiation was the cause of 10% of the cancers and leukemias (based on a faulty understanding of what the DD is, as discussed above) and the cause of 5 to 50% of the genetic diseases and deaths annually occurring in the United States. What Gofman and Tamplin failed to realize was that the NAS panel of eminent BEAR I geneticists actually failed to come to any quantitative consensus on the nature of the dose response in the low dose zone. In fact, Gofman and Tamplin would be misled by the BEAR I Genetics Panel [5] misrepresentation of the research record and, therefore, it can be legitimately argued that this BEAR I misrepresentation was ultimately responsible for their faulty methodological approach to risk assessment as it afforded Gofman and Tamplin the license and freedom to promote their LNT agenda.

The letter and statement by Sewall Wright in this paper is highly critical of the Gofman and Tamplin cancer risk assessments and is clearly important on its own merit. However, it may be interesting to speculate further on what may have happened if certain LNT deceptions had not occurred. For instance, had Gofman and Tamplin known that Wright's LNT-based estimate of radiation-induced mutational risk in humans was one of three estimates removed by the BEAR I Genetics Panel [5] for the expressed purpose of improving the statistical spread among estimates, Gofman and Tamplin may have acted with greater scientific objectivity and integrity in 1969 than they otherwise did. Similarly, had Gofman and Tamplin known about the cover-up results from the Russell lifespan and cancer study in 1959 instead of 35 years later [40], they may have again acted with greater scientific integrity in 1969 than they otherwise did. These are only two examples of the many LNT deceptions documented over the past decade or so [22, 48, 65, 66]. The examples above illustrate specifically how the early LNT deceptions of BEAR I and Russell spawned and gave rise to the later new deceptions of Gofman and Tamplin.

10. Conclusions

In light of the above assessment of the activities of Gofman and Tamplin, it becomes obvious why the Atomic Heritage Foundation declared that Gofman was instrumental in the adoption of the linear no-threshold model and in the wider acceptance of the somatic risks of ionizing radiation. What they didn't say was that he achieved this goal via an amazing causal nexus:

- being a highly regarded graduate student of Nobel Laureate Glenn Seaborg, who discovered plutonium for the atomic bomb;
- becoming a physician;
- being a very accomplished UCal/Berkeley professor, with much knowledge of the physical and biological sciences;
- being appointed by AEC Director Seaborg as an Associate Director of the Livermore in charge of radiation health effects;
- becoming involved with the Monticello nuclear power plant dispute on the side of opponents;
- having an inspired and talented colleague (Tamplin);
- being the ultimate insider/now called whistle blower that appealed to the media, assuring widespread publicity;
- linking his publicity with his traits of being highly provocative and unabashedly challenging;
- being hard-working;
- being extremely courageous;
- being prone to exaggerate risks and misrepresent the facts to manipulate societal fears of dreaded diseases such as leukemia, cancer, birth defects and other genetic diseases in order to win his political battles (which he did) while not being forced to be subjected to rigorous peer review.

The historical foundations of LNT are incomplete without a recounting of the Gofman-Tamplin affair and an accounting of its effects on the process of cancer risk assessment up to the present time. Since these two scientists weren't key researchers, members of key committees such as BEAR I, or major decision makers, Gofman and Tamplin have obviously been overlooked regarding their huge impact on the history of LNT. However, this unique partnership of courageous risk takers challenged the administrative, scientific, and political leadership at the highest levels, despite their numerous flaws, limitations, and questionable ethics. The LNT story is also incomplete without grasping the significance of the impact of the misrepresentation of the scientific record by the BEAR I Genetics Panel on their uncertainties for estimating radiation-induced mutation at low doses and the cover up actions of Russell and their effects on the Gofman and Tamplin story. Further, if Gofman and Tamplin had known that the 1960 BEAR Genetics and Medical Panels were strongly against low-dose extrapolation for cancer risks, the Gofman-Tamplin affair may never have occurred.

Nonetheless, the Gofman-Tamplin affair did occur as it stoked the public fears that provided the political rationale and incentive for the US Congress to instruct the NAS to form the BEIR I Committee in 1970. The BEIR I Committee, which was packed with pro-LNT scientists, not surprisingly recommended the EPA adopt and use the LNT dose-response model in assessing cancer risks from radiation exposures. Having been so well served by the NAS BEIR I Committee, the EPA created a succession of BEIR Committees (I - VII, thus far) that have "rubber stamped" LNT for over a half century, despite an ever-accumulating mass of countervailing evidence [18]. Such a succession of BEIR Committees may never have occurred without the unique story and impact of John Gofman and Arthur Tamplin.

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Letter to the Editor
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Pleural Mesothelioma Following Unusual Exposure to Asbestos: A Cluster in the Production and Maintenance of Electric Motors for Hand Tools

A recent re-evaluation of 364 cases of malignant mesothelioma (MM) without any apparent exposure has identified or suggested a possible source of exposure in a significant proportion [1]. In 2005, we suggested producing and maintaining motor components for electric hand tools as a potential source of occupational asbestos exposure in two workers who died from pleural MM [2]. The first one was ascribed to an unknown exposure to asbestos by the classification proposed by the National Mesothelioma Register [3]. Still, the appearance of a second case suggested the need for in-depth studies on this process, which made it possible to highlight a previously ignored exposure to asbestos, confirming the occupational origin of both MM cases in the turning and grinding spare parts for power tools in a factory employing about 25 workers and operating since 1972. This led to their INAIL insurance compensation.

The two workers' jobs required the manipulation of components of electric motors – rotors – coated with an insulating phenolic resin also reinforced with chrysotile asbestos (until 1991), found in samples of the insulating material analyzed after the appearance of the second case. In the following years, the systematic epidemiological surveillance led to identifying two more cases of pleural MM: one was a worker who performed the same tasks as the previous two. Table 1 summarizes the clinical and anamnestic characteristics of the 4 cases detected up to 2020.

The judicial autopsies performed on the latter two workers (cases 3 and 4) made it possible to analyze the residual lung content of asbestos bodies (in light microscopy, MOCF) and asbestos fibers (in scanning electron microscopy, SEM) at the ARPA Electronic Microscopy Centre in Milan with the methodology described elsewhere [4, 5]. In the third case, a total of 16,000,000 asbestos fibers/g dry tissue were found, 87% amphiboles and 11% chrysotile. In the 4th case, amphibole fibers equal 330,000 and 700 asbestos bodies/g dry tissue. For all workers, possible occupational exposure to asbestos before or after the one that occurred in this factory and non-occupational exposures were excluded; in addition, none had received chest radiotherapy.

We would like to comment on some aspects of this pleural mesothelioma cluster: (i) the death of 3 workers occurred much earlier than predictable according to the average life expectancy; (ii) the duration of asbestos exposure was short (min. four, max. seven years) in three out of four cases; (iii) four cases of pleural mesothelioma in a small cohort of workers suggest a high risk, even though part of the pieces was wetting and grinding; (iv) the lung fiber load detected in the third case is high and mainly composed of amphiboles. This result suggests a relevant cumulative exposure and is not limited to chrysotile alone, confirming that the intensity of exposure in this factory could be high, at least for the task of assembly and maintenance. Unlike turning and grinding, operations did not take place with the wetting of the machined components.

In conclusion, even the cluster of cases of pleural mesothelioma described here corroborates the fact that occupational asbestos exposure, initially thought

Table 1. Characteristics of malignant mesothelioma (MM) cases in four out of 25 workers from a small factory producing and maintaining motor components for electric hand tools.

ID#	Birth	Diagnosis	Death	Age	Histology	Task	From	To	Latency
1	1955	2002	2003	48	bifasic	turning and grinding	1973	1980	29 y
2	1960	2003	2005	45	epithelioid	turning and grinding	1974	1979	29 y
3	1957	2007	2010	53	bifasic	assembly and maintenance	1973	1977	34 y
4	1951	2019	2019	68	bifasic	turning and grinding	1974	2018	45 y

to be absent or improbable, can instead be defined as sure after (i) in-depth checks on the working methods and materials used and (ii) biological indicators of cumulative dose, qualitative-quantitative expression of previous exposure.

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CONFLICT OF INTEREST: P.G.B. e S. L. served as a consultant for the prosecutor or (P.G.B.) for the victims' families in litigations concerning asbestos-related diseases. R.G. e A.S. no conflict of interest.

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La Medicina del Lavoro

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Domenico Germanò (1934-2022)

Nello scorso mese di settembre è venuto a mancare il Prof. Domenico Germanò, Emerito di Medicina del Lavoro presso l'Università degli Studi di Messina. Nato a Scido (RC) il 1° febbraio 1934, si è laureato in Medicina e Chirurgia nel 1958 e ha cominciato a frequentare l'Istituto di Medicina del Lavoro dell'Università di Messina per il conseguimento del diploma di Medico di fabbrica. Ha iniziato la sua carriera accademica nel 1966 come docente in Medicina del Lavoro, giungendo al ruolo di professore Ordinario nel 1986. Nel 1978 gli è stata affidata la Direzione dell'Istituto di Medicina del Lavoro, che ha mantenuto fino al 2006, anno del suo ritiro in quiescenza. Nello stesso Ateneo è stato Direttore della Scuola di Specializzazione in Medicina del Lavoro dal 1982.

Sin dagli anni Sessanta ha intrapreso linee di ricerca innovative nella Medicina del Lavoro e pionieristiche per l'epoca, tra cui la caratterizzazione della pneumoconiosi da pomice, a quei tempi sconosciuta, che è stata per la prima volta inquadrata a Messina e denominata "liparosi", e la classificazione delle patologie correlate al lavoro nelle miniere di zolfo.

Ha inoltre collaborato alla redazione del testo di Medicina del Lavoro coordinato dal Prof. Duilio Casula (1993).

Del Prof. Germanò sono vive nella memoria di quanti lo hanno conosciuto le capacità organizzative di rilevanti eventi scientifici nazionali e internazionali, che ce lo fanno ricordare ancora oggi per le sue ineguagliabili doti di generosità e ospitalità. In particolare, a conclusione della carriera ha organizzato Patologia da silice. Linee Guida SIMLII (Lipari, 2004) e il 65° Congresso Nazionale SIMLII (Giardini Naxos, 2002).

Negli anni di servizio è stato Vice Presidente della Società Italiana di Medicina del Lavoro e Igiene industriale, Presidente della Società Mediterranea di Medicina del Lavoro, Socio fondatore e Presidente della Sezione Siculo-Calabra della Società Italiana di Medicina del Lavoro.

Grazie alle grandi capacità relazionali e di mediazione, alla costante disponibilità e capacità di ascolto, al profondo senso di appartenenza istituzionale, il prof. Germanò ha conquistato stima e apprezzamento anche in ambito nazionale.

Ricordiamo il Prof. Domenico Germanò come Maestro e amico dall'elevato spessore umano e culturale; la sua improvvisa perdita lascia un vuoto incolmabile e una grande tristezza in quanti hanno avuto il privilegio di conoscerlo e lavorare con lui.

Concettina Fenga
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5. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. Lyon, France: IARC, 2010: 92

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