Caries lesions progression in adults:

a prospective 2-year cohort study

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ABSTRACT

Background: Dental caries is one of the most prevalent chronic non-communicable diseases worldwide. There is a lack of evidence, especially in adult populations, documenting caries disease progression considering lesion severity, activity, and tooth surface-level characteristics.

Research question: In a sample of adults, to what extent do primary active caries lesions progress after two years compared with inactive caries lesions, based on their severity, surface and tooth type?

Methods: A prospective cohort study data set in Belarusian adults were used. Subjects aged 18-64 years old with 20 or more natural teeth were included in the study. The participants were clinically examined twice within an interval of two years and completed a self-reported questionnaire focusing on socio-demographic and oral health-related behaviours information. Clinical examinations were performed in standardized conditions using a dental chair, dental light, suction device, mouth mirror, and dental probes. One trained and calibrated examiner evaluated caries lesions using the ICDAS (severity) and the Nyvad (activity) diagnostic systems. The primary outcome was caries lesions' progression. The lesion is classified as 'progressed' if it turned to a more advanced severity stage, was restored, or missing/extracted due to caries. Results are presented descriptively with reporting counts, percentages, and mean values. A multilevel Poisson regression model was utilized to estimate the rate of caries lesions' progression over the study period.

Results: 322 adults out of 495 completed clinical examinations at baseline and two years later, with an attrition rate of 35%. Intra-examiner Cohen's kappa for caries lesion severity (ICDAS) was: 0.64 (CI 95%, 0.67-0.63); for caries lesion activity (Nyvad): 0.69 (CI 95%, 0.72-0.66). At the baseline, mean number of active caries lesions was 9.0 (±11.4 SD) for DS_{1-6}, and 5.6 (±9.7 SD) for DS_{5-6} thresholds. The prevalence of active DS_{1-6} and DS_{5-6} lesions at the baseline was 83.8% and 64.8% respectively. After adjustment for age, gender, baseline caries experience, tooth and surfaces type, the rate ratio (RR) for $ICDAS_{1+2}$, active and $ICDAS_{3+4}$, active lesions' progression was 1.78 (CI 95%, 1.40, 2.24) and 1.96 (CI 95%, 1.53, 2.51) respectively compared to $ICDAS_{1+2}$, inactive lesions; the RR for $ICDAS_{3+4}$, inactive lesions' progression was 1.06 (CI 95%, 0.79, 1.42). The RR for progression of caries lesions located on proximal surfaces was 1.56 (CI 95%, 1.29, 1.87) and for progression of pit and fissure lesions, the RR was 1.36 (CI 95%, 1.11, 1.66) compared to smooth surface lesions.

Conclusion: Active caries lesions were more likely to progress to more severe conditions than inactive lesions. Micro-cavitated lesions/shadows ($ICDAS_{3+4}$) were more likely to progress than non-cavitated lesions ($ICDAS_{1+2}$). Molar and premolar lesions were more likely to progress compared to anterior lesions. Pitts and fissures and proximal lesions were more likely to progress compared to smooth surface lesions. Thus, caries lesions' severity and activity, as well as the tooth and surface type need to be considered when planning caries treatment decisions in caries active adults.

RÉSUMÉ

Contexte : La carie dentaire est l'une des maladies chroniques non transmissibles les plus répandues dans le monde. Il y a un manque de preuves, en particulier dans les populations adultes, documentant la progression de la carie en tenant compte de la gravité de la lésion, de l'activité et des caractéristiques au niveau de la surface de la dent.

Question de recherche : Dans un échantillon d'adultes, dans quelle mesure les lésions carieuses actives primaires progressent-elles après deux ans par rapport aux lésions carieuses inactives, en fonction de leur gravité, de leur surface et du type de dent?

Méthodes : Un ensemble de données d'étude de cohorte prospective chez des adultes biélorusses a été utilisé. Les sujets âgés de 18 à 64 ans avec 20 dents naturelles ou plus ont été inclus dans l'étude. Les participants ont été cliniquement examinés deux fois dans un intervalle de deux ans et ont rempli un questionnaire axé sur des informations sociodémographiques et sur les comportements liés à la santé buccodentaire. Les examens cliniques ont été effectués dans des conditions standardisées à l'aide d'un fauteuil dentaire, d'une lumière dentaire, d'un dispositif d'aspiration, d'un miroir buccal et de sondes dentaires. Un examinateur formé et calibré a évalué les lésions carieuses à l'aide des systèmes de diagnostic ICDAS (sévérité) et Nyvad (activité). Le critère de jugement principal était la progression des lésions carieuses. La lésion est classée comme « évoluée » si elle s'est transformée en un stade de gravité plus avancé, a été restaurée ou manquante/extraite en raison de caries. Les résultats sont présentés de manière descriptive avec des décomptes, des pourcentages et des valeurs moyennes. Un modèle de régression de Poisson à plusieurs niveaux a été utilisé pour estimer le taux de progression des lésions carieuses au cours de la période d'étude.

Résultats : 322 adultes sur 495 ont terminé les examens cliniques du départ et deux ans plus tard, avec un taux d'attrition de 35 %. Le kappa de Cohen intra-examinateur pour la gravité des lésions carieuses (ICDAS) était : 0.64 (IC 95 %, 0.67-0.63) ; pour l'activité des lésions carieuses (Nyvad) : 0.69 (IC 95 %, 0.72-0.66). Au départ, le nombre moyen de lésions carieuses actives était de 9.0 (± 11.4 SD) pour DS_{1-6} et de 5.6 (± 9.7 SD) pour les seuils DS_{5-6}. La prévalence des lésions actives DS_{1-6} et DS_{5-6} à l'inclusion était de 83.8 % et 64.8 % respectivement. Après ajustement pour l'âge, le sexe, l'expérience carieuse initiale, le type de dents et de surfaces, le rapport entre les taux (RT) pour $ICDAS_{1+2}$, actif et $ICDAS_{3+4}$, la progression des lésions actives était de 1.78 (IC 95 %, 1.40, 2.24) et 1.96 (IC 95 %, 1.53, 2.51) respectivement par rapport à $ICDAS_{1+2}$, lésions inactives; le RT pour $ICDAS_{3+4}$, progression des lésions inactives était de 1.06 (IC 95 %, 0.79, 1.42). Le RT pour la progression des lésions carieuses situées sur les surfaces proximales était de 1.56 (IC 95 %, 1.29, 1.87) et pour la progression des lésions des fosses et fissures, le RT était de 1.36 (IC 95 %, 1.11, 1.66) par rapport aux lésions de surface lisse.

Conclusion : Les lésions carieuses actives étaient plus susceptibles d'évoluer vers des conditions plus sévères que les lésions inactives. Les lésions/ombres micro-cavitaires ($ICDAS_{3+4}$) étaient plus susceptibles de progresser que les lésions sans cavité ($ICDAS_{1+2}$). Les lésions molaires et prémolaires étaient plus susceptibles de progresser que les lésions antérieures. Les fossettes et les fissures et les lésions proximales étaient plus susceptibles de progresser que les lésions de surface lisse. Ainsi, la gravité et l'activité des lésions carieuses, ainsi que le type de dent et de surface doivent être pris en compte lors de la planification des décisions de traitement des caries chez les adultes actifs carieux.

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DEDICATION

I would like to dedicate this work to the soul of my father Abou-Bakr Abdalla, who has always been a role model for me, for his unconditional love, support, unending encouragement, wise advice, and prayers.

CONTRIBUTION OF AUTHORS

Hoda Abdalla, MSc candidate, developed the aims, wrote the research protocol, prepared the data, performed the statistical analysis, and wrote the thesis.

Paul Allison, Professor, McGill University, guided the project development, developed the research question and objectives of the study designed, supervised this study, and reviewed thesis writing.

Svetlana Tikhonova, Faculty lecturer, McGill University, involved in research question development, protocol development, management of the project and guiding the data cleaning, data analysis, thesis writing, and data interpretation.

Sreenath Arekunnath Madathil, Assistant Professor, McGill University, guided data cleaning and analytic approach development, and guided the statistical analysis.

Natallia Pustavoytova, Dentist, Belarus, recruited the subjects, organized, and conducted all data collection.

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

CAMBRA	Caries Management by Risk Assessment
CBCT	Cone Beam Computed Tomography
CRA	Caries Risk Assessment
CI	Confidence Interval
DMFS	Decayed, Missed, Filled Surfaces
DMFT	Decayed, Missed, Filled Teeth/ permanent teeth
dmfs	decayed, missed, filled surface/ primary teeth
DT	Decayed Teeth
DFS	Decayed, Filled surfaces
ICDAS	International Caries Detection and Assessment System
ICCMS	The International Caries Classification and Management System
LAA	Lesion Activity Assessment
OR	Odds Ratio
pH	Potential of Hydrogen
RR	Rate Ratio
SD	Standard Deviation
US$	United States dollar
WHO	World Health Organization

1. INTRODUCTION

Dental caries is one of the most prevalent noncommunicable disease, affecting 60-90% of children and the vast majority of adults globally (Kassebaum et al., 2017). It is a multifactorial disease induced by the metabolism of dietary, fermentable carbohydrates by oral bacteria. The interaction between saliva, oral hygiene, dietary habits, fluoride exposure, and other biological determinants affects biofilm composition and metabolism which finally may affect the activity status of caries lesions, particularly whether they would progress or not (Pitts et al., 2017). Thus, caries lesion activity should be considered in the management of dental caries. Active lesions require active intervention to stop the disease progression while arrested, non-active lesions do not require disease treatment unless there is a need to restore esthetics and function and/or a need to engage in therapies aimed at preventing re-activation of the disease (J. D. B. Featherstone et al., 2021).

Importantly, it is crucial to have a more sophisticated approach for diagnosing caries lesions that permits their detection but also assesses their severity and activity. Assessment of severity and activity provides an essential information for caries management decision-making (Nyvad & Baelum, 2018). Visual/visual-tactile examination methods permit differentiation between non-cavitated and cavitated lesions, as well as between active and inactive lesions, and these are the pivotal elements on which the most effective caries management options can be chosen (Guedes et al., 2018; Nyvad & Baelum, 2018). There are two promising visual/visual-tactile caries diagnostic methods: the Nyvad (B. Nyvad et al., 1999) and ICDAS (Ismail et al., 2007) systems were developed and recommended for use in research and clinical practice (Pitts et al., 2017).

Despite these two systems being developed some time ago, in the last 2 decades, most researchers did not assess lesion activity during their clinical examinations (Ismail et al., 2015). In addition, almost all epidemiological data concerning dental caries in adults come from cross-sectional studies, which lack information regarding caries lesion behaviour and rates of progression over time (Abbass et al., 2019; Dye et al., 2015; Laajala et al., 2019). Given these observations, it is essential to have studies longitudinally assessing caries lesions in adults using contemporary diagnostic criteria to evaluate lesion severity and activity, taking into account tooth and surface type. This project investigates how caries lesions may or may not progress according to their severity and activity status in the adult population when they are detected using contemporary visual-tactile caries diagnostic systems.

2. COMPREHENSIVE REVIEW OF THE RELEVANT LITERATURE

Research background and rationale

2.1. Dental caries

2.1.1. Definition and disease determinants

Dental caries is a multifactorial, chronic, non-communicable disease that involves interactions between the tooth surface, biofilm, sugars, and host factors (Pitts et al., 2017). Dental caries is a result of an ecological alteration in the balance of the normally beneficial oral microorganisms, induced by modification of lifestyle factors and oral environment (Pitts et al., 2017). It consists of rapidly alternating periods of demineralization and remineralization of tooth surface, which, if net demineralization prevails over enough time, can results in the initiation of caries lesions at specific sites on the tooth surfaces (Pitts & Zero, 2016; Pitts et al., 2017). The process may also be complicated by salivary dysfunction, insufficient preventive planning, and social determinants of health, therefore, it is not conducive to a single preventive or therapeutic treatment that fits all patients (Featherstone et al., 2021). Any part of the tooth that is exposed to tooth biofilm accumulation throughout an individual's lifetime is susceptible to dental caries (Takahashi &

Nyvad, 2016). Lesions develop where biofilms are left to mature and stay for prolonged periods of time and result in prolonged drops in the pH of the local environment, resulting in demineralization of the local tooth surface (Featherstone, 2004).

It has been known that oral health conditions are directly linked to the socioeconomic situation (Watt & Sheiham, 2012). Individuals react to psychological stress and adverse social situations by smoking, consuming too much alcohol, excessive eating, and taking risks (Elstad, 1998). The effects of the social environment on oral health behaviours are linked to how people of different socioeconomic conditions with diverse personal propensities, vulnerabilities and capabilities interact with each other and their economic and social conditions (Watt & Sheiham, 2012). Disadvantaged individuals have increased exposure to occupational and environmental health threats and stress in work and life, which results in lower self-esteem and poorer social communications and social support. While, the most advantaged have better health conditions than the less advantaged (Starfield et al., 2002). Individuals in the higher social ranks are enjoying good health than those immediately below them in a stepwise manner. This stepwise gradient in health consequences also appears across the life course from childhood to adulthood (Starfield et al., 2002). Focussing only on a person's lifestyle overlooks the network of social effects on health and thus detaches behaviours from their social context (Diez Roux, 1999). Evaluation of individual behaviour change interventions has demonstrated that although short-term changes in behaviour can be achieved, these changes are rarely maintained in the longer term in the absence of alterations to the social environments that drive the behavioural patterns in the population (Medicine et al., 2001). Failure to target the environmental determinants goes some way to answering why behavioural preventive measures in dental settings are insufficient in modifying long-term oral health outcomes (Watt & Sheiham, 2012).

While the proximal cause of dental caries is increased consumption of sugary foods (Blostein et al., 2020; Lopes-Gomes et al., 2021), it is also important to consider more distal determinants such as household food insecurity (Lee et al., 2020), age, smoking (Petersson & Twetman, 2019), level of education, income level, frequency of tooth brushing and exposed root surfaces(Guan et al., 2020). Additionally, uninsured adults have a higher prevalence of dental caries and lower mean number of restorations than insured adults (Peres et al., 2020). Furthermore, it was noticed that people living in rural areas had 40% higher prevalence of untreated dental caries than those living in urban areas (31.7%; (Peres, Thomson, et al., 2020).

2.1.2. Caries process description

Dental caries disease is a result of a dysbiosis in tooth biofilm (Fontana et al., 2018). When sugar is frequently ingested or salivary secretion is insufficient to neutralize the produced acids by bacteria in tooth biofilm, these may lead to prolonged periods of low pH in the biofilm (Takahashi & Nyvad, 2008). The frequent and prolonged pH drops can lead to dysbiosis in tooth biofilm when acidogenic and aciduric bacteria prevail (Takahashi & Nyvad, 2008). This microbial shift may alter the demineralization/ remineralization equilibrium from net mineral gain to net mineral loss. Thus, under the low pH conditions, a biofilm–tooth interface becomes undersaturated with calcium and phosphate, enabling the initiation of demineralization of the tooth surface. This increases the porosity of enamel by enlarging the gaps between the enamel crystals, which permits acid to spread deeper into the tooth resulting in subsurface demineralization (Pitts et al., 2017). However, if fluoride is available in the biofilm fluid, and the pH is higher than 4.5, hydroxyapatite is broken down while fluorapatite is created. So, enamel dissolution is diminished since a certain amount of hydroxyapatite is replaced by fluorapatite (Cury & Tenuta, 2009). The dissolution of the tooth substance elevates the degree of saturation of calcium and phosphate, which prevents further demineralization of tooth surface (Featherstone, 2004). On top of this interaction at the tooth surface, the buffering process of saliva can neutralize the biofilm acids as soon as sugar is removed from the oral cavity by salivary clearance. Therefore, the pH of biofilm fluid becomes neutral and saturated enough with calcium, phosphate and fluoride ions that prevents demineralization and starts remineralization (Featherstone, 2004). Given this highly dynamic process that occurs each time we consume refined carbohydrates, it is crucial to balance the pathological elements that promote the initiation and progression of dental caries with the protective processes that can prevent or halt caries progression. Protective factors promote remineralization and lesion arrest, whereas pathological factors change the balance toward caries disease progression (Pitts & Zero, 2016).

2.2. Caries disease burden and epidemiology

Dental caries is one of the most prevalent non-communicable diseases affecting 2.5 billion adults and 621 million children globally (Kassebaum et al., 2015). Dental caries has been estimated to affect almost every individual during their adult life, affecting on average from 5 to 10 teeth/ person (Abbass et al., 2019). Kassebaum et al., reported that the age standardized prevalence of untreated caries in permanent teeth was 34.1%, while in deciduous teeth, the age-standardized prevalence of untreated caries was 7.8% (Kassebaum et al., 2017). The distribution of untreated caries is not the same all over the world (Kassebaum et al., 2015). Based on a report from the National Health and Nutrition Examination Survey conducted in the US in 1999-2004, nearly 5% of American adults aged (20-64) had no teeth and 92% had dental caries experience in their permanent teeth. The mean DMFT and DMFS of American adults aged (20-64) were 3.28 and 13.65 respectively.

The Canadian Health Measures Survey (2007- 2009) reported that the prevalence of dental caries was 57%, 58% and 96% for children, adolescents, and adults respectively (CCPA report: www.policyalternatives.ca, 2011). It was stated that the number of decayed and missing teeth as well as oral pain were highly concentrated in poorer groups in Canada (Ravaghi et al., 2013). Ramraj and coworkers analyzed data collected from the Canadian Health Measures Survey (2007-2009) and found that about 12 million Canadians had unmet dental treatment requirements, and two million had an urgent requirement (Ramraj et al., 2012). Notably, dental caries develops in a constant rate during childhood, adolescence, and adulthood (Broadbent et al., 2013). In the cross-sectional study conducted among middle-aged Finish adults, it was found that almost all participants (99%) had enamel caries ($ICDAS_{1-3}$), and 40% had dentin caries ($ICDAS_{4-6}$). Additionally, $ICDAS_{4-6}$ lesions were markedly located in upper bicuspids and lower molars (Laajala et al., 2019). Among Australian adults aged 15–34 years, the prevalence of dental caries was 62% and increased to 88% among those with age range 55–74 years (Peres, Ha, et al., 2020). The prevalence of dental caries and missing teeth was 68% and 81% respectively among Chinese adults aged 65-74 years (Liu et al., 2013). Average DMFT values among Tibetan adults were 7.62, 12.46, 21.38 for age groups 35-44, 45-64, 65-74 respectively (Guan et al., 2020). Oscarson et al. assessed dental caries among Norwegian adults aged 20-79 years old and found that mean DMFT was 15.1, mean DS_{3-5} and DS_{1-5} levels were 0.8 and 3.8 respectively (Oscarson et al., 2017). In Vietnam, the prevalence of dental caries among adults (≥18 years) was 81.3% with a mean DMFT of 4.98 (Loc Giang et al., 2011). According to an epidemiological survey conducted in Belarus in 2017, 100% of the population aged 35-44 had caries disease (D_3 level); average DMFT values were 15.2 (range: 12.5 – 16.1) and 25.3 (range: 23.7 – 26.2) in population groups aged 35-44 and

65-74 years respectively. The percentage of edentulous people aged 65 -74 was 16% (range: 12.9 – 18.7(Matveev et al., 2018).

2.3. Consequences of dental caries

As caries lesions progress, they result in tooth pain, eating difficulties, and tooth loss if management does not occur in the early stages. In children, caries can result in delayed language development and affect their concentration in school (Barasuol, 2020; Moure-Leite, 2011). It was reported that 25% of American aboriginal school children avoided laughing or smiling, and 20% avoided meeting other people because of the appearance of their teeth (Naidoo et al., 2001). Dental caries and its' consequences may affect adolescents' nutrition, growth, development, oral health, general health, and quality of life (Liu et al., 2013). Moreover, in adults, caries-related tooth loss can diminish quality of life, limiting food choices and impeding social interaction (Kassebaum et al., 2015). Dental pain impacts families in various ways by increasing the consumption of analgesics and increasing the costs of dental treatment (Barasuol, 2020). Furthermore, oral diseases, including caries, are among the costliest diseases to manage in developed countries (Petersen, 2005). In 2010, it was found that global economic impact of dental caries amounted to US$442 billion (Listl et al., 2015). In Canada, it was estimated that total expenditures on dental services amounted to $13.6 billion in 2015. The expenditures were estimated at $12.7 billion and $846 million for private-sector and public-sector respectively. Moreover, the total health care expenditures in Canada were estimated at $219.2 billion, meaning that dental expenditures make up about 6.2% of all health care spending (CDA, 2017).

2.4. Contemporary caries diagnosis and management approach

2.4.1 Dental caries diagnostic systems

Dentists usually detect dental caries using visual-tactile examination with the aid of radiographic assessments (Kidd & Fejerskov, 2004). Traditionally, caries lesion detection was only based on presence or absence of cavitation (Abbass et al., 2019; Dye et al., 2015). To report dental caries experience, the DMF index is used to count the number of Decayed, Missing and Filled teeth/surfaces per person (DMFT/ DMFS)(Robinson, 2017). DMFT/S can be utilized at different diagnostic thresholds which represents caries experience of both current and past caries disease (Kühnisch et al., 2008). Current WHO basic methods criteria (WHO, 2013) record caries lesions at the cavity level, which results in underestimation of caries experience by ignoring the early enamel lesions (Ismail, 2004a; Pitts et al., 2017).

It is crucial to have data on the progression pattern of caries lesions to help policy makers to implement prevention plans to arrest or control carious lesions especially for young children and adults who experience rapid progression of dental caries (Pitts et al., 2017). The evolution and refinement of diagnostic methods had been affected by the need to clinically differentiate between sound and diseased tooth tissue based on different severity stages and activity of dental caries lesions. Detecting the caries disease at earlier stages and assessing their activity offers the opportunity for non-surgical caries management aimed at caries lesions' arrest, with the goal of protecting the tooth structure from entering a lifelong cycle of restorations (Pitts et al., 2017). Contemporary visual/visual-tactile examination is the most commonly utilized technique for detecting caries lesions. This is a relatively easy method, allowing detection of lesions and assessment of their severity and activity at one point in time. These items of information are essential for appropriate caries management planning (Nyvad & Baelum, 2018). Ismail reviewed 29 different visual criteria for detecting dental caries lesions (Ismail, 2004b). The author found that almost half of the methods recommended cleaning and/or drying the teeth before the examination otherwise the risk of missing lesions (false negatives) increases. In this review evaluations were carried out to determine whether these diagnostic criteria (visual/visual tactile) 1) measure a range of severity stages of lesion progression; 2) differentiate between active and inactive signs of the lesions; 3) include differentiation between carious and non-carious lesions; and 4) clearly define the terms for measuring the caries process. The author found 13 systems either measured active/inactive early and cavitated lesions, 9 systems assessed early as well as cavitated caries lesions, and 11 systems gave clear descriptions on how to differentiate non-caries from caries lesions. In addition, the review took into account whether the teeth were cleaned and/or dried before clinical assessment and the usage of dental probes. Based on this evaluation criteria (content validity) there were five diagnostic systems (Ekstrand et al., 1998; Fyffe et al., 2000; Ismail et al., 1992; Nyvad et al., 1999; Pitts et al., 1997) which met 8 out of 10 criteria. This review showed that there is a lack of consistency for many systems developed to assess the caries disease process, also this review was utilized as a rational to develop the International Caries Detection and Assessment System (ICDAS; (Ismail, 2004b). A comparative analysis of accuracy of several diagnostic methods used for detecting initial caries (visual or visual-tactile examination based on detailed criteria, fluorescence, radiographic imaging, cone beam computed tomography (CBCT), optical coherence tomography and transillumination, and electrical conductance or impedance) was conducted based on data from five Cochrane diagnostic test accuracy systematic reviews (Walsh et al., 2022). The network metanalysis has shown that the summary sensitivity estimates were highest for visual-tactile methods, such as ICDAS, the Ekstrand-Ricketts-Kidd, and the Nyvad systems (0.83, CI 0.77- 0.87). Similarly, sensitivity estimates were 0.83, (CI 0.66-0.92) for electrical conductance or impedance, followed by fluorescence (0.76, CI 0.68- 0.82) and transillumination (0.76, CI 0.63, 0.86) methods, while radiographic imaging had the lowest sensitivity (0.50, CI 0.40 - 0.59). The summary specificity estimates were more similar across the diagnostic methods and varied from 0.72 (CI 0.44, 0.89) for electrical conductance or impedance, to 0.89 (CI 0.83, 0.93) for radiographic imaging. The summary specificity for visual-tactile diagnostic methods was 0.81 (CI 0.73, 0.87). The certainty of evidence was graded as low due to selection bias, unexplained heterogeneity (inconsistency), and a large proportion of studies on extracted teeth (indirectness). The authors concluded that when robust and detailed visual or visual-tactile diagnostic criteria are used, there is a little additional benefit for the use of novel technologies (e.g., light fluorescence, transillumination, etc.) for caries lesions detection (Walsh et al., 2022).

2.4.2. ICDAS (International Caries Detection and Assessment System)

The ICDAS system was developed by an international group of cariologists and epidemiologists, who presented a new modality for the assessment of dental caries based on systematic reviews of the literature and other evidence sources (Ismail, 2007). The system was adjusted in 2002 and again in 2005. The ICDAS measures the caries lesions severity (depth) based on tooth surface characteristics which are matched with the histological depth of the lesions. The primary requirement for applying the ICDAS system is the examination of clean and dry teeth. Moreover, a ball-ended probe that is utilized to check the surface texture and to remove any remaining plaque is used (Pitts et al., 2013). ICDAS consists of a two-digit identification score system. The first digit records the status of the surface whether it is restored, sealed, or crowned, while the second digit uses a seven-point ordinal scale from 0-6 to evaluate lesion severity based on measurement of first visual change in the enamel to extensive dentinal cavitation (Ismail, 2007). The ICDAS system has demonstrated both content and criterion validity and showed good sensitivity (0.63 - 0.82) and specificity (0.63 - 0.94) for occlusal surfaces (Braga, F. M. Mendes, et al., 2010). The ICDAS has a detailed protocol, it is an open system that can be modified over time, and it is available and well described on a website (https://www.iccms-web.com). The outcome of using the ICDAS system can be converted to DMFT(S) scores to allow comparison with previous studies results (Pitts et al., 2013). The ICDAS also involves lesion activity assessment system (Pitts et al., 2011). To date, there are various methods of caries lesion activity assessment systems for the ICDAS (Ismail et al., 2013; Velo et al., 2019). In an in-vitro study another caries activity assessment system proposed to be used with ICDAS criteria (Lesion Activity Assessment, LAA) demonstrated an area under the curve equal to 0.84, with the highest combined sum of specificity and sensitivity at 1.67 (Ekstrand et al., 2007). When ICDAS criteria were used with the LAA system by calibrated examiners, the inter-examiner kappa value was 0.89 (Braga, K. Ekstrand, et al., 2010) and the intra-examiner kappa value was 0.63 and 0.90 (Braga et al., 2009; Ekstrand et al., 2007).

A two-year cohort study was conducted among children to investigate the risk of active caries lesions progression to more severe conditions, in comparison to inactive lesions by using ICDAS system (Guedes et al., 2014). In this study the caries lesion activity was assessed as follows:

- for ICDAS $_{1\text{-}3}$ the lesion is considered active if: the enamel surface is whitish/yellowish opaque with loss of luster, feels rough when the tip of the probe is moved gently across the surface, and the lesion is in a plaque stagnation area.
- For ICDAS $_{1\text{-}3}$ the lesion is considered inactive if: the enamel surface is whitish, brownish, or black; and if the enamel is shiny and feels hard and smooth when the tip of the probe is moved gently across the surface.
- for ICDAS $_{4}$ all lesions evaluated at his level are considered to be active.
- for ICDAS $_{5\text{-}6}$ the lesion is considered active if the cavity feels soft or leathery on gently probing the dentine and inactive if the cavity is shiny and feels hard on gentle probing.

The authors found that non-cavitated active caries lesions showed higher risk of progression than inactive caries lesion in primary dentition (Guedes et al., 2014). Furthermore, children presented with a greater number of active lesions and with higher caries experience at baseline showed higher risk of developing new lesions. It was concluded that the caries activity evaluation system associated with ICDAS presents predictive and construct validity in the assessment of occlusal caries lesions among deciduous teeth, however this system did not have predictive validity in smooth surfaces.

The feasibility of the ICDAS severity assessment criteria was evaluated in two studies among dentists. The results demonstrated that dentists were able to utilize the ICDAS scoring system in their routine practice and that it required 5 to 14 minutes to inspect adult patients (Bonner et al., 2011; Ormond et al., 2010). The comprehensive severity assessment scale might be beneficial in caries epidemiological research. However, having a scale with six scores for assessment of lesion depth, together with the additional coding system for activity, could increase the difficulty to be utilized in everyday dental practice (Tikhonova et al., 2014).

The International Caries Classification and Management System (ICCMS) is linked with the ICDAS system to help dentists to integrate and develop caries management on both tooth and patient levels, involving caries risk status. This permits planning, managing, and reviewing caries in clinical practice (Pitts et al., 2014). Moreover, ICCMS utilizes ICDAS merged codes for the purpose of caries management, in which caries severity is categorized in to three stages: initial stage (ICDAS 1 and 2), moderate stage (ICDAS 3 and 4), and extensive stage (ICDAS 5 and 6) (Pitts et al., 2014). Moreover, the most recent caries lesions activity assessment approach suggested to be used within the ICDAS system is based on the Nyvad system (Nyvad et al., 1999; Nyvad & Baelum, 2018).

2.4.3. The Nyvad system

The Nyvad clinical caries diagnostic system reflects the dynamic nature of the caries process and is based on a concept of lesion activity assessment (Nyvad et al., 2003). The Nyvad system distinguishes between active and inactive carious lesions based on their visual-tactile surface features, along with determinations of caries lesion's depth (Nyvad et al., 1999). The system assesses lesion activity at the time of examination based on combining information about the presence of dental plaque, location, luster, texture and color of the caries lesion (Nyvad, 2004). Typical active enamel lesions appear whitish/yellowish opaque in color, look mat and feel rough on gentle probing, while active dentinal/root caries lesions feel soft or leathery on gentle probing and have a discoloured appearance. An inactive caries lesion appears shiny and feels smooth (enamel) or hard (dentinal/root) on gentle probing (Nyvad et al., 1999). The explorer is recommended to be utilized with a gentle touch (with no or very light pressure) to assess the caries lesion surface integrity or texture and to eliminate dental plaque, if required (Nyvad et al., 1999). The use of the Nyvad system requires clean and dry teeth as well as an excellent light source. Based on the results of previous studies that were carried out on primary and permanent teeth by calibrated examiners, the intra-examiner kappa values for the Nyvad criteria were 0.74-0.95, and the inter-examiner kappa values were 0.58-0.94 (Braga, F. M. Mendes, et al., 2010; Braga et al., 2009; Nyvad et al., 1999). The sensitivity of the Nyvad system reflecting lesion severity is (0.69 - 0.90) and their specificity is (0.74 - 0.94) (M. M. Braga et al., 2010; Braga et al., 2009). The predictive validity of Nyvad system was confirmed by showing that active, non-cavitated lesions presented a higher risk to become cavitated or treated by restoration than inactive, non-cavitated lesions in children (Nyvad & Baelum, 2018). The Nyvad system is a beneficial tool in caries lesions management at both individual lesion and at patient levels, especially in low-caries communities, where most of the caries experience is at the non-cavitated stage of development (Nyvad & Baelum, 2018). In addition, the Nyvad criteria are recommended for use in clinical research and, more relevantly, in clinical practice to help clinicians in caries risk assessment and in selection of management options, as well as for observing caries lesions over time (Nyvad & Baelum, 2018). The Nyvad criteria use a simple coding system that connects the caries scores with their subsequent management decisions. However, Nyvad lacks detailed classifications of caries lesions severity, which could be beneficial for epidemiologic studies of caries (Tikhonova et al., 2014).

A previous study assessed the clinical performance of two visual scoring criteria (Nyvad and ICDAS-LAA) for detecting caries lesion severity and assessing caries lesion activity on occlusal surfaces (Braga, K. Ekstrand, et al., 2010). The authors found both scoring systems showed high inter-examiner reproducibility (kappa values were 0.94 and 0.91 for Nyvad and ICDAS-LAA respectively) and validity (sensitivity values were 0.89 and 0.92 for Nyvad and ICDAS respectively; specificity values were 0.81and 0.79 for Nyvad and ICDAS respectively at the D1 threshold) to detect and estimate caries lesion depth in primary teeth. However, the ICDAS-LAA overestimated the caries activity assessment of cavitated lesions in comparison with the Nyvad system (Braga, K. Ekstrand, et al., 2010). Drancourt and coworkers systematically reviewed the different utilized methods for assessment of caries lesion activity and recommended Nyvad criteria or ICDAS-LAA to be the ‘reference standard’ for further in vivo studies (Drancourt et al., 2019).

2.5. Management of caries

Traditionally, caries management relied on complete removal of carious tissue and restoring the cavity (Schwendicke et al., 2019). This surgical treatment method of dental caries is no longer considered the optimal model for dental care because it only focuses on signs and symptoms of advance stages of the disease and does not take into account the etiological factors of the disease. The treatment outcome basically depends on the success of dental fillings, some of which have limited longevity (Moraschini et al., 2015), while ignoring the factors that resulted in the lesion in the first place. It was reported that the average longevity of resin-based composite restorations was only 6 years (Sunnegårdh-Grönberg et al., 2009) and their failure may be due to recurrent disease and/or breakdown/fracture of the restoration. This confirms that surgical only management of caries is unsatisfactory for disease control (Yu et al., 2021). The contemporary caries management approach should be person-centered based on minimizing the caries risk factors and promoting protective factors with the aid of behavior modification and long-term follow-ups (J. Featherstone et al., 2021; Yu et al., 2021).

Featherstone et al., 2021 reviewed four most commonly used caries risk assessment (CRA) methods (CAMBRA (Featherstone, Alston, et al., 2019; Featherstone, Crystal, et al., 2019), Cariogram (Bratthall & Hänsel Petersson, 2005), American Dental Association (ADA, 2011, 2021), and American Academy of Pediatric Dentistry (Dentistry, 2020)), and found that the Cariogram and the CAMBRA CRA tools are equally useful for assessing the future disease risk. It was suggested that dentists should choose the CRA tool that helps them to establish individualized, successful caries management modality to empower their patients with knowledge to help them to improve their health choices (Featherstone et al., 2021).

Recently, intervention strategies for the management of carious lesions were classified as follows: 1) Non-invasive methods, which include fluoride use, biofilm control measures and dietary control through sugar restrictions; 2) Micro-invasive approaches for management of incipient enamel carious lesions by using sealants or resin infiltration techniques; 3) mixed approaches (e.g., non-restorative cavity control, the Hall Technique; and 4) Invasive strategies for non-cleansable cavitated caries lesions by using either hand excavators or rotary instruments to selectively remove carious tissue and then restoring function and/or aesthetics (Schwendicke et al., 2019). The goal of treating carious lesions is to control their activity through non- or micro-invasive management strategies and apply a surgical approach for more advanced stages of caries in circumstances when non-surgical strategies are not suitable (Desai et al., 2021). On the tooth surface level, lesion activity, presence of cavitation and lesions' cleansability are the main factors to be considered to determine caries intervention thresholds (Schwendicke et al., 2019). Inactive lesions do not usually need any intervention (in some cases, fillings might be placed to restore function and aesthetics), while active lesions do. Non-cavitated and cleansable cavitated lesions should be managed non- or micro-invasively. Non-cleansable cavitated carious lesions usually require invasive/restorative treatment to restore function and aesthetics of the tooth (Schwendicke et al., 2016).

2.6. Caries lesions progression

Studying dental caries progression is important, as it helps to identify those periods in life when risk of disease is high along with the information about how various types of caries lesions progress. All this information is essential to indicate when and where an intervention is needed (Ferreira Zandoná et al., 2012). The distribution of untreated caries is not the same all over the world (Kassebaum et al., 2015). This confirms the importance of studying the natural history of dental caries in different countries, populations and groups within populations to collect information that help better understand the disease process in each of these communities. It was previously noticed that the burden of untreated dental caries is shifting from childhood to adulthood and untreated caries is peaking later in life, in adults rather than children (Kassebaum et al., 2015). It was stated that older people (50+) are a caries-active group, showing new caries lesions at a rate which is at least as great as that of adolescents (Thomson, 2004). In such older groups, different teeth and/or tooth surfaces may be more likely to progress compared to younger groups, thus dental caries progression requires assessment in different age groups to predict which caries lesions are most likely to progress to cavitation (Ferreira Zandoná et al., 2012).

Almost all the available epidemiological caries data among adults is from cross-sectional studies (Carta et al., 2015; García-Cortés et al., 2009; Liu et al., 2013; Loc Giang et al., 2011; Peres, Ha, et al., 2020). To obtain a comprehensive image of the natural history of caries experience in adult populations the following guidelines were proposed: (a) the study sample be representative; (b) all permanent teeth be considered in the analysis; (c) separate evaluation for missing teeth i.e., whether it was extracted due to caries or missing for some other causes; and (d) using prospective longitudinal study design (Broadbent et al., 2006). Moreover, it also requires that the subjects being studied have been randomly chosen from the general population because patients who regularly use dental care tend to differ in various important aspects from those who do not (Thomson, 2004).

In children, it was reported that caries progression from the enamel surface to dentin (in posterior permeant molars) can be a relatively slow process, sometimes taking up to 4 years (Arrow, 2007). This gives a relatively long window of opportunity for preventive efforts to be implanted to minimize the likelihood of disease progression to stages in which restorative intervention is inevitable (Arrow, 2007).

Vanderas et al. investigated caries lesion progression at different stages of proximal caries in children, aged 6-8 years old by using bitewing radiographs taken once yearly over a period of 4 years (Vanderas et al., 2006). Children were divided to three caries experience groups based on baseline mean DMFS/dmfs as follows: low experience (mean DMFS/dmfs = 0.91); moderate experience (mean DMFS/dmfs = 5.31); and high experience (mean DMFS/dmfs = 16.52) groups.

It was found that the group with high caries experience at baseline experienced increased risk of developing caries in the sound proximal surfaces of posterior deciduous teeth and experienced faster progression of the external half of enamel lesions in first permanent molars and posterior deciduous teeth over a period of four years.

Piva et al. utilized ICDAS criteria to assess the incidence and progression of carious lesions in 3-4 years old children in Brazil (Piva et al., 2017). At the baseline evaluation they noted the prevalence of dental caries at $ICDAS_1$ level was 89.9% while the prevalence at $ICDAS_4$ level was 26%. Additionally, children who had non-cavitated lesions at baseline had less risk (RR 0.48 [CI 0.37,0.62]) to progress compared to children who had cavitated lesions (ICDAS≥3).

Another study assessed caries lesion progression using the ICDAS system in a 2-year cohort study conducted among Brazilian children aged between 12 to 59 months old (Guedes et al., 2014). The authors found that nearly 10% of surfaces with active $ICDAS_{1+2}$ scores and 50% of surfaces with $ICDAS_3$ scores became frankly cavitated, restored, or missing after 2-years, while 6.2% and 34.3% of non-cavitated and micro-cavitated inactive lesions respectively became frankly cavitated, restored, or missing over the same period. Additionally, they reported that: 1. active non-cavitated caries lesions on occlusal surfaces had approximately 60% higher risk to progress to a more severe status (RR=1.64 (CI=1.10, 2.47)) and about twofold higher risk to become frankly cavitated, restored, or missed (RR=2.04 (CI=1.11, 3.74)) compared to inactive non-cavitated occlusal caries lesions; 2. active caries lesions and lesions with higher initial ICDAS scores showed higher risk of progressing (RR for $ICDAS_2$ and $ICDAS_3$ were 1.98 [CI=1.25, 3.14] and 6.28 [CI=3.79, 10.39] respectively); 3. occlusal surface caries showed higher risk to progress than smooth surfaces (RR=2.20 [CI=1.55, 3.13]); and 4. caries lesions on second primary molars teeth presented higher risk of progression than lesions in primary first molars and canines (Guedes et al., 2014). In Detroit, Mich., USA (Ismail et al., 2015) a two-year cohort study was conducted to assess caries lesion progression in children (aged 0–5 years) based on lesion severity using the ICDAS criteria, while caries lesion activity was not assessed. The authors found: 1) tooth surfaces with baseline caries lesions were at a higher rate of caries progression than sound surfaces; 2) surfaces with baseline $ICDAS_{1+2}$ scores were 9.6 times more likely to progress to $ICDAS_3$ and $ICADS_4$ levels at follow-up than sound surfaces (RR = 9.6, 95% [CI = 7.0– 13.1]); 3) the relative rate (RR) of caries progressing from baseline initial caries ($ICDAS_1$ & $ICDAS_2$) to extensive caries ($ICDAS_5$& $ICDAS_6$) and restorative treatment were 6.1 (95% CI = 4.7-7.9) and 4.7 (95% CI = 3.1-6.9) respectively compared to sound surfaces; 4) surfaces with baseline moderate caries ($ICDAS_3$ & $ICDAS_4$) had 20.6 times the risk of caries progressing to extensive caries compared to sound surfaces (95% CI = 16.4– 25.9), while, it (surface with $ICDAS_3$ & $ICDAS_4$) had 7.0 times the rate of caries progression to become restored compared to sound surfaces was (95% CI = 4.5–10.9); and finally, 5) the RR of caries progressing from initial caries in primary teeth to extensive caries was 2 times higher in smooth surfaces (9.5, 95% CI = 6.9–13.1) compared to pit and fissure surfaces (5.2, 95% CI = 3.8–7.1).

A 4-year cohort study conducted among children aged between 5 and 13 years in Puerto Rico, USA (Ferreira Zandoná et al., 2012). In this study, clinical examination was conducted using the ICDAS criteria for recording lesion severity, while the activity scores were based on the following signs: surface luster (opaque or translucent), texture (rough or smooth), and location (in a plaque stagnation area or not). Moreover, bitewing radiographs were taken once a year. The mean DMFS/dmfs for different ICDAS levels at baseline was calculated as follows: 16.3 (± 13.2), 8.5 (± 9.2), and 7.6 (± 8.7) for $ICDAS_1$, $ICDAS_3$, and $ICDAS_5$ respectively. Caries lesion progression to cavitation was varied based on baseline location, severity, and activity scores. Only 3% of sound surfaces progressed during the follow up period. Nearly 19%, 32%, and 68% of the surfaces scored as ICDAS $_1$, ICDAS $_2$, and ICDAS $_3$ respectively become cavitated. All surfaces with ICDAS$_4$ were considered active and were most likely to cavitate during the study period.

A one-year cohort study (Zenkner et al., 2016) assessed caries incidence and progression on sound occlusal surfaces in comparison to surfaces with inactive enamel lesions in Brazilian children and adolescents (aged 7-15 years). The clinical examinations of enamel changes on occlusal surfaces of permanent molars were performed after air drying following these criteria: (0) normal enamel translucency after air drying; (1) opaque enamel with dull-whitish surface (active lesion, non-cavitated /cavitated); and (2) shiny appearance of the surface of the opaque area with different degrees of brownish discoloration (inactive lesion, non-cavitated /cavitated). After 1 year, only 11% of the children showed caries lesion progression identified by presence of at least one active lesion on sound or inactive enamel lesion surfaces at the baseline examination. Caries incidence was 2.6 % in sound surfaces, while caries progression in inactive non-cavitated and cavitated lesions were 2.6% and 16.6 % respectively. The authors noticed that the only predictor for caries incidence and progression after 1 year was the existence of easily visible plaque on occlusal surfaces (OR 2.73, CI 1.01-7.41; (Zenkner et al., 2016).

Broadbent et al. conducted a birth cohort study in New Zealand using WHO criteria (1997) to assess caries progression in permanent dentition to the age of 32 years. They categorized participants according to caries experience (DMFS) at the baseline into high (15%), medium (43%), and low (42%) caries experience groups. By the age of 32 years, the mean DMFS was 5.4, 18.6, and 42.3 in the three groups respectively. Additionally, no one had lost their teeth due to caries by the age of 18 years. However, there was a marked increase in tooth loss due to caries in all groups by the age of 32 (Broadbent et al., 2008). Moreover, the authors found after following the participants to the age of 38; that the number of tooth surfaces affected by dental caries increased by approximately 0.8 surfaces/ year. Additionally, at age 38, among caries-affected teeth, it was noticed that the number of affected surfaces were highest in upper third molars followed by upper second premolars (Broadbent et al., 2013).

The effect of age, period and cohort effects on caries experience in permanent teeth was evaluated by utilizing epidemiological, cross-sectional data series from four different countries (England and Wales, United States, Japan, and Sweden). They found a strong influence of age appeared in caries experience. DMFT scores were markedly increased from childhood through to adolescence, thereafter, there was a greater increase in adulthood. In England and Wales, the DMFT score increased from 11.4 (CI = 8.9-14.0) in the 16 to 24 years group to 21.4 (CI = 17.8 -24.9) in 75 years or older group, in the United States from 5.3 (CI = 0.1-10.6) in the 6 to 14 years group to 17.9 (CI = 14.2- 21.5) in the 85 years or older group, in Japan, from 3.6 (CI = 1.6-5.7) in the 5 to 14 years group to 24.0 (CI = 22.2-25.9) in the 75 years or older group, and in Sweden from 7.1 (95% CI = 3.2, 11.0) in the 10 years group to 21.4 (CI = 17.6-25.2) in the 80 years group (Bernabe & Sheiham, 2014). Furthermore, the authors noticed that the pattern of dental caries increases with age, however, there was a relatively small decrease across time and generations (period and cohort effects) in all of the four countries evaluated (Bernabe & Sheiham, 2014).

In Norway, Dobloug and Grytten used previously collected longitudinal data that included individuals born during the period 1940–1989 who received regular dental care in the public dental services to study subjects aged 14-72 years. They assessed caries lesion progression by counting the number of teeth per patient with cavitated primary carious lesions and secondary caries lesions. During the period 2003-2012, they observed a significant reduction in caries lesion progression in all the birth cohorts especially in the older cohorts. The mean number of carious teeth (DT) were

0.65, 0.62, 0.47, 0.54, and 0.68 for 1940-1949, 1950-1959, 1960-1969, 1970-1979, and 1980-1989 respectively. They noted that mean DT component was low and presented only minor variation among the reported birth cohorts. Almost 10.7% of subjects in the oldest birth cohort and 14.3% of subjects in the youngest birth cohort had no cavitated caries lesions each year during the whole 10-year follow up (DT=0). Additionally, nearly half of the participants had no cavitated caries for at least eight years (Dobloug & Grytten, 2015).

Kassebaum et al. systematically reviewed all available observational studies (longitudinal or cross-sectional) that reported untreated cavitated caries lesions (either primary or secondary), regardless of language, geography, age, gender or publication status, from 1980 to 2010. They reported that every year the number of new cases of dental caries in a hundred participants was fifteen in deciduous teeth and twenty-seven in permeant teeth. Moreover, the prevalence and incidence of untreated caries lesions stayed constant worldwide during the twenty-year study period (Kassebaum et al., 2015).

(Mejàre et al., 1998) longitudinally assessed the pattern of caries development in teenagers and adolescents by using bite-wing radiographs performed annually for 10 years in Sweden. They found a slow but continuous rise in both enamel and dentin proximal caries. At the age of 21, about 29% of all posterior proximal surfaces had enamel caries, 14% had dentin caries, and 5% were filled. Also, the occlusal and proximal surfaces of the first molars represented 60% of all restored surfaces. Moreover, the percentage of participants with no proximal caries detected using bite-wing radiographs decreased from 71% (at the age12-13) to 28% (at the age 20-21).

Chaffee and coworkers used a retrospective cohort study design with a mean follow up period of 539 days (±257) to evaluate caries occurrence by baseline caries risk category for subjects aged 18 years or older (Chaffee et al., 2015). The mean difference between low and extreme risk groups was more than two affected teeth per 18 months. The caries incidence Risk Ratio was 1.28 (CI 1.10, 1.52) and 1.52 (CI 1.23, 1.87) for high and extreme risk groups respectively.

In a five-year cohort study conducted among adults aged 20-59 years in Japan using WHO criteria, it was observed that the incidence of coronal caries decreased with aging while the incidence of root caries markedly increased. The rate of incidence of coronal caries in adults aged 20–29 years was 77.3% while it was 61.5%, 64 %, and 60 % for the age group 30–39, 40–49, and 50–59 years respectively. Also, they noticed that the odds of new coronal caries was reduced with increased age (OR=0.7, CI 49, 0.99), while the odds of new coronal caries was increased when number of coronal DFS ≥ 10 (OR=2.9, CI 1.28–6.59), and number of sound teeth ≥ 20 (OR=3.4 CI 1.63–7.22; (Sugihara et al., 2014).

2.7. Rationale

It is clear from this brief review of the literature on caries epidemiology, diagnosis and disease progression that contemporary caries management approaches need to focus on nonsurgical treatment methods and caries risk assessment (Desai et al., 2021; Yu et al., 2021), and that these approaches must rely on a contemporary understanding of carious lesion development and progression and need diagnostic systems able to determine carious lesions from their very early beginning, along with their depth and activity (Guedes et al., 2014; Pozos-Guillén et al., 2021). Moreover, a good caries diagnostic system should be linked with management methods (Nyvad & Baelum, 2018). These requirements are essential for achieving the best possible dental health results. Visual/visual-tactile examination is one of the principal methods currently utilized in clinical practice that permits differentiation between non-cavitated and cavitated lesions, as well as between active and inactive lesions. These are the pivotal elements on which the best caries management options can be chosen (Guedes et al., 2014; Nyvad & Baelum, 2018). There are two promising visual/visual-tactile caries diagnostic methods: the Nyvad (B. Nyvad et al., 1999) and the ICDAS (Ismail et al., 2007), which have been developed and recommended for use in research and clinical practice (Pitts et al., 2017). The most recently updated ICDAS system integrates caries lesions' activity assessment based on the Nyvad criteria (ICCMS; (Pitts et al., 2014).

Most of the caries-related data in adults are based on cross-sectional studies, which lack information regarding caries lesion behaviour and rates of progression over time (Abbass et al., 2019; Dye et al., 2015; Laajala et al., 2019). A number of existing cohort studies in adults are using outdated caries diagnostic criteria (e.g., WHO) which do not take into account different stages and activity of caries lesions (Broadbent et al., 2013; Chaffee et al., 2015; Dobloug & Grytten, 2015; Sugihara et al., 2014). Moreover, most of cohort studies on caries progression with the use of contemporary caries diagnostic systems (e.g., ICDAS, Nyvad) were performed in children (Ferreira Zandoná et al., 2012; Guedes et al., 2014; Ismail et al., 2015; Nyvad et al., 2003; Zenkner et al., 2019). Some of these studies are only based on the lesions severity assessment (Ismail et al., 2015), some studies focus on severity and activity assessment of caries (Ferreira Zandoná et al., 2012; Guedes et al., 2014; Zenkner et al., 2019), and few of them take into account the surface and tooth type when assessing lesions' progression (Guedes et al., 2014; Ismail et al., 2015).

Therefore, it is essential to conduct more studies longitudinally assessing caries lesions behaviour in adults, using contemporary diagnostic criteria, taking into account their severity and activity as well as tooth and surface type. This will help to better understand the pattern of caries disease progression and to efficiently plan caries management options.

Accordingly, the objective of this study was to investigate if caries lesions with different severity, activity and locations progress differently in a sample of adults, over a period of two years when the nested data effect is taken into account (individual, tooth, surface levels).

2.8. Research question:

In a sample of adults, to what extent do primary active caries lesions progress after 2 years compared with inactive caries lesions, based on their severity, surface and tooth type?

The overall objectives of this study

1. To estimate the extent to which caries lesions' severity (non-cavitated/micro-cavitated + shadow) and activity (active/inactive) status is associated with caries lesion progression.

2. To estimate the extent to which tooth type (molar/premolar/anterior) and tooth surface type (smooth, proximal, surfaces with pits and fissures surfaces) is associated with caries lesion progression.

Hypothesis one: more severe lesions are more likely to progress than less severe lesions.

Hypothesis two: active lesions are more likely to progress than inactive lesions.

Hypothesis three: pitts and fissures and proximal surface lesions are more likely to progress than smooth surface lesions.

Hypothesis four: caries lesions located on molars and premolars are more likely to progress than lesions located on anterior teeth.

3. BODY OF THE THESIS

3.1. Methodology

3.1.1. Study design

A prospective cohort study design was used to examine caries lesion progression among the adult population in Belarus within two years of follow-up. Factory workers from Borisov city who agreed to consent underwent two clinical examinations by the same trained and calibrated examiner at the dental office at the factory's medical center at the baseline and two years. Before the start of the examination, each participant filled out a self-reported questionnaire that contained sociodemographic (e.g., age, sex, income, and level of education) and oral health behaviors related questions (e.g., tooth brushing frequency, F toothpaste, number of dental visits, frequency of sweet intake, etc). The research project was approved by the Ethical committee of Belarusian State Medical University, Protocol № 13; 16.12.2011.

3.1.2. Population and sample frame

The study population is adults living in Borisov city, Belarus. Borisov is a midsize city located 74 km northeast of the capital, Minsk. Its' population is around 145,000. The study participants were recruited from Borisov industrial assembling factory, Belarus. The selection of this factory was based on feasibility to recruit adult population and presence of dental office on site. Inclusion criteria were caries-free and caries-active adults aged 18 years or older with 20 or more natural teeth. Exclusion criteria were: 1) individuals with orthodontic appliances; 2) individuals with multiple teeth with hypocalcified enamel; 3) individuals with systemic disorders with oral manifestation.

3.1.3. Recruitment and consent

Participants were informed that their participation was voluntary, they can withdraw from the study at any time, and they were free to ask any questions regarding their oral health. The factory administration notified all factory workers about the possibility of participating in a research project on caries lesions progression. The participants were invited to attend the factory's dental office for dental examinations while coming for routine preventive medical checkups organized in the factory's medical center. The research team provided a schedule for dental examinations to the administration and a local factory manager facilitated the organization of a flow of dental examinations. Each participant who was available in a particular day for medical exam and agreed to take part in the project was notified when to come to dental office for the examination. The data collection was anonymous, kept confidential, and stored securely. A written consent was given to each participant that contain all information about the study. Each consented participant was asked to visit the dental clinic twice over two years. During the baseline examination, all participants received detailed oral hygiene instructions and if any restorations were needed, they were advised to have an appointment with a dentist in a state or private dental clinic.

3.1.4. Training and calibration of the examiners

All clinical examinations were performed by one trained and calibrated examiner for the use of the ICDAS and Nyvad diagnostic systems. At the baseline and follow up examinations first ten subjects from the cohort were examined twice with an interval of one week to calculate intra-examiner reliability using Kappa statistics.

3.1.5. Caries diagnostic criteria and examination

Caries lesion severity was assessed using the ICDAS diagnostic system (Ismail, 2007) and caries lesion activity was assessed using the Nyvad system (Nyvad, 1999). All examinations were done using the same dental unit with its light source, dental mirrors, ball-ended WHO probe was used for the ICDAS, and a sharp standard dental explorer for the Nyvad criteria. Before each examination, dentist cleaned the teeth surfaces for each participant by using circular brush attached to low-speed handpiece to remove plaque. All surfaces were first examined wet and then air-dried. The dental probe was gently used to remove tooth biofilm if needed, to assess tooth surface integrity and texture. If one surface had both active/inactive lesions or different severity stage, then it was listed as active with the greater severity (i.e., active>inactive; cavitation> microcavity>intact surface). We identified seven surfaces for upper molars (occlusal mesial fissure, occlusal distal fissure, mesial, distal, lingual groove, and lingual and buccal surfaces), six surfaces for lower molars (occlusal, mesial, distal, buccal fissure, buccal surface, and lingual surface), five surfaces for upper premolars and canines (occlusal, mesial, distal, buccal, and lingual surfaces), five surfaces for upper incisors (mesial, distal, buccal, lingual groove and lingual surfaces), and four surfaces for lower incisors (occlusal, mesial, distal, buccal, and lingual surfaces). Therefore, the maximum number of the tooth surfaces examined per participant was 174 surfaces. The overall examination period for all subjects for baseline or for the follow up examination took approximately one month.

3.1.5.1. The ICDAS diagnostic system

The ICDAS codes are presented in two digits: the first code represents restoration, while the second code represents severity. ICDAS severity codes were ordinally arranged into six categories in which code 1 represents the first visible carious change in enamel, while code six represents extensive cavitation. When dental examiner can't examine the surface, surface was missing because of caries, surface was missing because of other reason, or unerupted tooth the following codes were used respectively: 96, 97, 98, 99.

3.1.5.2. The Nyvad system

The Nyvad system was used for lesion activity assessment (Nyvad & Baelum, 2018). Caries lesion was considered active if it was located in a plaque stagnation area, showed a whitish/yellowish color with loss of lustre and rough/soft feeling of the surface with gentle probing using a sharp explorer. Inactive caries lesions had the following characteristics: located away from the gingival margin, showed whitish/brown/black shiny appearance and were smooth/hard with gentle probing using a sharp explorer (Nyvad et al., 1999). The activity code was the third code added to the first two ICDAS codes.

After 2-year, participants were reexamined by the same trained calibrated dentist blinded to the baseline data. At the end of second appointment, participants were provided with a detailed information about the status of their teeth and treatment needs.

3.1.6. Statistical Analysis

The intra-examiner's agreement for caries lesions diagnosis was assessed using Cohen's Kappa coefficient (Landis & Koch, 1977). The Kappa and 95% CI was calculated separately for caries lesions' severity (ICDAS criteria) and for caries lesions' activity (Nyvad criteria) assessment.

3.1.7. Descriptive statistics:

The data about sociodemographic status (e.g., age, gender, occupation, income, and education) and caries related behavioral factors (e.g., frequency of tooth brushing, fluoridated toothpaste, dental visits) were presented separately for participants who completed baseline examination, the follow up examination and for those who dropped out. For all of these three groups the caries experience and caries prevalence on different diagnostic thresholds were reported. The sample distribution of continuous variables was described using means and standard deviations (SD) and for the categorical data counts and percentages were used.

3.1.8. Caries experience and prevalence

The caries experience was calculated on a surface and tooth levels as mean DMFS and DMFT for two diagnostic thresholds: $ICDAS_{1-6}$ and $ICDAS_{5-6}$. In addition, mean number of active caries lesions and their prevalence on tooth and surfaces levels for two diagnostic thresholds (D_{1-6} active and $D_{5\text{-}6}$ active) were calculated.

3.1.9. Caries lesions transition

When describing the progression of caries lesions, we focused only on primary non-cavitated, micro-cavitated and shadow lesions at the baseline (ICDAS codes 1, 2, 3 and 4), active and inactive. To describe the transition of caries lesions in 2-years follow up, we used the following categories: sound (ICDAS 0), all ICDAS severity codes from 1 to 6, Restored, or Missed due to caries. To represent the data transition descriptively (Table 1) we merged the baseline ICDAS $_{1\ \text{and}\ 2}$ codes to one category ($ICDAS_{1+2}$) to represent non-cavitated lesions and the ICDAS $_{3\ \text{and}\ 4}$ codes to one category ($ICDAS_{3+4}$) to represent micro-cavitated/shadow lesions. We kept the differentiation at the baseline for $ICDAS_{1+2}$ and $ICDAS_{3+4}$ to active and inactive lesions categories. In addition, the lesions transition was presented based on surface type (pits and fissures, proximal and smooth) and tooth type (molars, premolars, anterior).

3.1.10. Outcome evaluation

Our outcome was caries lesions' progression presented as a dichotomous variable: 1. progress or 2. not progress. The primary caries lesion, active or inactive was considered as 'progress' in 2-years follow up if it transited to more advanced stage (e.g., from ICDAS $_2$ to ICDAS $_3$), was restored, or missed due to caries. The primary caries lesion, active or inactive was considered as 'not progress' in 2-years follow up if it regressed to less severe stage or had the same severity stage. Note, that non-plausible transition scenarios (e.g., ICDAS $_{3+4}$ become sound) were classified as 'not progress'. We calculated the caries lesions progression variable for each surface by subtracting the follow-up value from the baseline value. If the resultant value is greater than zero, we considered this surface as progressed; if the value ≤ zero, we considered it as not progressed (see Table 1).

Table 1. Caries lesions transition: scoring lesions' progression outcome

Baseline lesion's severity and activity status	Sound= 0	ICDAS $_{1+2}$=1	ICDAS $_{3+4}$=2	Cavitated=3 (ICDAS $_{5+6}$)	Missing=4	Restoration=4
ICDAS $_{1+2}$ =1	-1	0	1	2	3	3
ICDAS $_{3+4}$=2	-2	-1	0	1	2	2

Progression codes: ≤ 0= no progression; > 0= progression

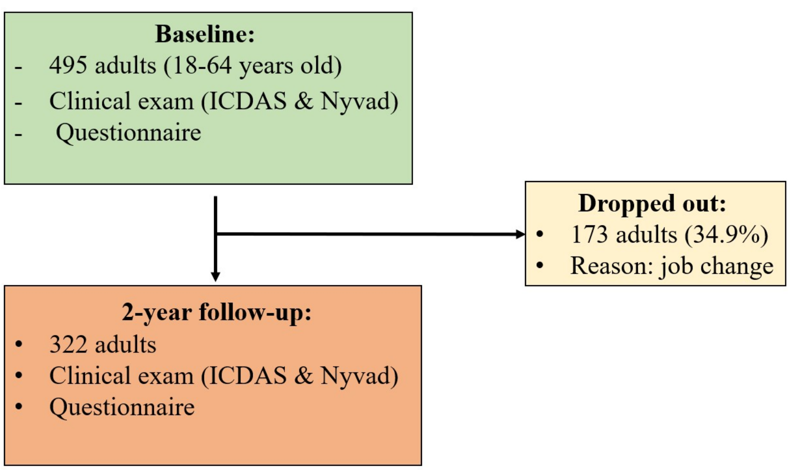
3.1.11. Regression analysis

We used generalized linear mixed effect model to estimate the association between baseline lesions' characteristics as exposure variables (caries severity, activity, tooth type, and tooth surface type status) and caries lesion's progression as an outcome variable. To account for the hierarchy in the data, we used multilevel Poisson regression implemented as mixed effect model with three levels. Level 1: surface (e.g., proximal, pits and fissures, smooth); Level 2: tooth (e.g., molars, premolars, anterior); Level 3: participant (e.g., ID-1, ID-2,…ID-322). Our measures of association and the corresponding 95% confidence intervals were estimated as Rate Ratios for caries progression from the above model. We run two separate multilevel Poisson regression models. In the first model, our exposure variable was primary lesion severity status at the baseline only (ICDAS $_{1+2}$ as a reference vs ICDAS $_{3+4}$), not taking into account the lesion's activity; tooth and surface types were considered as covariates. In the second model, our exposure variables were the interaction between severity and activity at the baseline (ICDAS $_{1+2}$ inactive as a reference vs ICDAS $_{3+4}$ inactive, ICDAS $_{3+4}$ active), surface type (smooth as a reference vs pits and fissures, proximal) and tooth type (anterior: as a reference vs molar, premolar). We utilized first an unadjusted Poisson regression analysis for both models to estimate the crude rate ratios of caries progression. Then these two models were adjusted for age, gender, and baseline caries experience (D1-6, active). We fitted a crude and fully adjusted model for each independent variable (e.g., baseline caries severity, baseline caries severity combined with activity, tooth type, and tooth surface type). All the analysis was performed with R version: 4.1.1 (2021-08-10).

3.2.Results

The intra-examiner's Cohen's kappa coefficient for caries lesion's severity (ICDAS) was: 0.64 (CI, 95% 0.67-0.63); for caries lesion activity (Nyvad): 0.69 (CI, 95% 0.72-0.66). At the baseline 495 adults were examined and 322 at the two-year follow up. The attrition rate (loss to follow up) was 34.9% (Figure1).

Figure 1: flowchart of the study



3.2.1. Sociodemographic and behavioral characteristics

The data about the sociodemographic status and caries-related behavioural factors presented for all participants at baseline, those who completed follow-up, and those who dropped out are presented in Tables 2 &3. At the baseline, 263 out of 495 of the participants were females (53.0%). Regarding the age at baseline, 276 (55.6%) adults were 35 to 54 years old; 152 (30.6%) were 18 to 34 years old, and 68 (13.7%) were 55 years and older. Most of the participants (95.2%) were from urban areas. Almost half (47.6%) of the participants at baseline reported graduation from college, and 28.6% received university education. Approximately 84% reported their monthly income did not exceed 300$. About 49% reported brushing their teeth twice or more /day. About 83% reported using fluoridated toothpaste. The vast majority of participants reported using neither fluoride rinse (90.3%) nor dental floss (84.7%). Almost 47% of the participants at baseline reported visiting their dentists in the last year for treatment reason and 17.3% for the dental emergency reasons.

3.2.2. Caries experience and prevalence

Mean $D_{1\text{-}6}$ MFS value at baseline was 84.5 (±37.5), while mean $D_{5\text{-}6}$ MFS was 63.1 (± 43). Mean $DS_{1\text{-}6}$, active and $DS_{5\text{-}6}$, active values at baseline were 9.0 (±11.4) and 5.6 (±9.7) respectively. The prevalence of active caries lesions at baseline was 83.8% and 64.8% on $DS_{1\text{-}6}$ and $DS_{5\text{-}6}$ levels respectively (Table 4).

3.2.3. Dropped out vs follow up participants

The participants who dropped out were younger than the participants who completed follow up examination (50% vs 20%, 18-34 years old, Table 2). Behavioural factors related to oral health in these two groups were not vastly different (Table 3). Participants who dropped out had higher mean number of active $DS_{1\text{-}6}$ caries lesions compared to the follow up group (10.9 (±12.8) vs 7.9 (±10.4)) and slightly higher prevalence of active $DS_{1\text{-}6}$ lesions (87% vs 82%, Table 4). Among the main reasons of dropouts were change of the job or the residence place.

3.2.4. Caries lesions' transition

The progression of primary caries lesions within the two-year follow up, based on their baseline severity and activity status, the surface involved and tooth type, is presented in Tables 5 and 6. Most active and inactive non-cavitated lesions (58.9% and 68.1% respectively) at baseline remained unchanged two years later. The progression of active non-cavitated lesions to become micro-cavitated/shadowed, frankly cavitated, restored, or missing due to caries (24.7% progressed) was almost 1.6 times more than inactive non-cavitated lesions, of which 15.9 % progressed. Regarding the micro-cavitated/shadowed lesions, 47.9% of inactive lesions and 43.1% of active lesions remained unchanged. The progression of active micro-cavitated/shadow lesions to more severe conditions was twice more as inactive micro-cavitated/ shadows lesions, with 31.5% of the former and 16.3% of the latter progressing (Table 5). Nearly 41.7% of active non-cavitated lesions located in pits and fissures progressed to more severe stages, while 21.8% and 20% of proximal and smooth surface lesions, respectively, progressed. About 41.4% of active micro-cavitated/shadowed lesions located on proximal surfaces progressed while only 24.5% and 22.8% of pit and fissure and smooth surfaces lesions, respectively, progressed (Table 5).

Among active non-cavitated lesions located in premolars, 32.6% progressed, while 24.9% and 17.2% of active non-cavitated lesions located in molars and anterior teeth, respectively, progressed. Furthermore, 43.8% of active micro-cavitated/shadow lesions located in premolars progressed while 31.3% and 25.4% of molar and anterior teeth lesions, respectively, progressed (Table 6).

Table 2: Socio-demographic characteristics of the participants at the baseline

	Baseline group (n=495), %	Follow up group (n=322), %	Dropped out group (n=173), %
Age group			
18-34	152 (30.6)	65 (20.2)	87 (50.3)
35-54	276 (55.6)	208 (64.6)	67 (38.7)
55 and older	68 (13.7)	49 (15.2)	19 (11.0)
Gender			
Male	232 (46.8)	135 (41.9)	97 (56.1)
Female	263 (53.0)	187 (58.1)	76 (43.9)
Missing	1 (0.2)	0 (0.0)	0 (0.0)
Living site			
Urban	472 (95.2)	304 (94.4)	168 (97.1)
Rural	22 (4.4)	18 (5.6)	4 (2.3)
Missing	2 (0.4)	0 (0.0)	1 (0.6)
Occupation			
No occupation	7 (1.4)	4 (1.2)	3 (1.7)
Manual	297 (59.9)	177 (55.0)	120 (69.4)
Non manual	190 (38.3)	141 (43.8)	49 (28.3)
Missing	2 (0.4)	0 (0.0)	1 (0.6)
Education			
High school	114 (23.0)	68 (21.1)	46 (26.6)
College	236 (47.6)	157 (48.8)	79 (45.7)
University	142 (28.6)	95 (29.5)	47 (27.2)
Missing	4 (0.8)	2 (0.6)	1 (0.6)
Monthly income			
up to 300 $	416 (83.9)	271 (84.2)	145 (83.8)
300-500 $	67 (13.5)	43 (13.4)	24 (13.9)
more than 500 $	4 (0.8)	2 (0.6)	2 (1.2)
Missing	9 (1.8)	6 (1.9)	2 (1.2)

Table 3: Oral health behaviours and caries experience among the participants at the baseline

	Baseline group (n=495), %	Follow up group (n=322), %	Dropped out group (n=173), %
Tooth brushing frequency			
Never	3 (0.6)	1 (0.3)	2 (1.2)
Less than daily	19 (3.8)	9 (2.8)	10 (5.8)
Once a day	223 (45.0)	143 (44.4)	80 (46.2)
Twice or more a day	243 (49.0)	164 (50.9)	79 (45.7)
Missing	8 (1.6)	5 (1.6)	2 (1.2)
Fluoridated toothpaste			
Yes	412 (83.1)	276 (85.7)	136 (78.6)
No	77 (15.5)	42 (13.0)	35 (20.2)
Missing	7 (1.4)	4 (1.2)	2 (1.2)
Fluoride rinse			
Yes	41 (8.3)	25 (7.8)	16 (9.2)
No	448 (90.3)	293 (91.0)	155 (89.6)
Missing	7 (1.4)	4 (1.2)	2 (1.2)
Flossing			
Yes	69 (13.9)	50 (15.5)	19 (11.0)
No	420 (84.7)	268 (83.2)	152 (87.9)
Missing	7 (1.4)	4 (1.2)	2 (1.2)
Dental visit, last 12 months			
Yes	346 (69.8)	238 (73.9)	108 (62.4)
No	143 (28.8)	80 (24.8)	63 (36.4)
Missing	7 (1.4)	4 (1.2)	2 (1.2)
The reason, last dental visit			
Regular check-up	167 (33.7)	106 (32.9)	61 (35.3)
Treatment, no emergency	233 (47.0)	159 (49.4)	74 (42.8)
Emergency pain	86 (17.3)	51 (15.8)	35 (20.2)
Missing	10 (2.0)	6 (1.9)	3 (1.7)

Table 4: Caries experience and prevalence among the participants at the baseline

	Baseline group (n=495)	Follow up group (n=322)	Dropped out group (n=173)
D_{1-6} MFT mean (± SD)	21.9 (±5.4)	22.5 (±5)	20.8 (± 5.9)
D_{5-6} MFT mean (± SD)	14.6 (±7.7)	15.7 (±7.3)	12.5 (±8.2)
D_{1-6} MFS mean (± SD)	84.5 (±37.5)	88.6 (±35.3)	77 (±40.3)
D_{5-6} MFS mean (± SD)	63.1 (±43)	88.6 (±35.3)	54.1 (±45.5)
DT_{1-6} Active mean (± SD	4.3 (±3.6)	3.9 (±3.4)	4.8 (±3.9)
DT_{5-6} Active mean (± SD)	1.3 (±2.1)	1.1 (±1.7)	1.7 (±2.45)
DS_{1-6} Active mean (± SD)	9.0 (±11.4)	7.9 (±10.4)	10.9 (±12.8)
DS_{5-6} Active mean (± SD)	5.6 (±9.7)	4.9 (±8.8)	6.8 (±10.9)
Prevalence (%), DS_{1-6} Active	83.8%	82.0%	87.3%
Prevalence (%), DS_{5-6} Active	64.8%	63.4%	67.6%

Table 5: Caries lesions' progression over two years according to lesions' severity/activity status and the surface type (participants, n=332)

Baseline lesion severity /activity status	Surfaces, n (baseline)	Follow up, 2 years			
		Sound (n, %)	ICDAS $_{1+2}$ (n, %)	ICDAS $_{3+4}$ (n, %)	ICDAS $_{5+6}$/ Restoration/missing (n, %)
ICDAS $_{1+2}$					
Pits and fissures					
Inactive	1699	209 (12.3)	1242 (73.1)	101 (5.9)	147 (8.7)
Active	84	19 (22.6)	30 (35.7)	20 (23.8)	15 (17.9)
Proximal					
Inactive	2585	370 (14.3)	1754 (67.9)	212 (8.2)	249 (9.6)
Active	119	16 (13.4)	77 (64.7)	5 (4.2)	21 (17.6)
Smooth					
Inactive	1169	294 (25.1)	719 (61.5)	45 (3.8)	111 (9.5)
Active	230	36 (15.7)	148 (64.3)	17 (7.4)	29 (12.6)
All					
Inactive	5453	873 (16.0)	3715 (68.1)	358 (6.6)	507 (9.3)
Active	433	71 (16.4)	255 (58.9)	42 (9.7)	65 (15.0)
ICDAS $_{3+4}$					
Pits and fissures					
Inactive	242	10 (4.1)	73 (30.2)	131 (54.1)	28 (11.6)
Active	94	3 (3.2)	22 (23.4)	46 (48.9)	23 (24.5)
Proximal					
Inactive	116	10 (8.6)	30 (25.9)	44 (37.9)	32 (27.6)
Active	116	10 (8.6)	20 (17.2)	38 (32.8)	48 (41.4)
Smooth					
Inactive	47	12 (25.5)	10 (21.3)	19 (40.4)	6 (12.8)
Active	57	5 (8.8)	8 (14.0)	31 (54.4)	13 (22.8)
All					
Inactive	405	32 (7.9)	113 (27.9)	194 (47.9)	66 (16.3)
Active	267	18 (6.7)	50 (18.7)	115 (43.1)	84 (31.5)

Table 6: Caries lesions' progression over two years according to lesions' severity/activity status and the tooth type (participants, n=332)

Baseline lesion severity /activity status	Surfaces, n (baseline)	Follow up, 2 years			
		Sound (n, %)	ICDAS $_{1+2}$ (n, %)	ICDAS $_{3+4}$ (n, %)	ICDAS $_{5+6}$/ Restoration/missing (n, %)
ICDAS $_{1+2}$					
Molars					
Inactive	3072	440 (14.3)	2133 (69.4)	197 (6.4)	302 (9.8)
Active	329	54 (16.4)	193 (58.7)	31 (9.4)	51 (15.5)
Premolars					
Inactive	1316	215 (16.3)	889 (67.6)	85 (6.5)	127 (9.7)
Active	46	6 (13.0)	25 (54.3)	6 (13.0)	9 (19.6)
Anterior					
Inactive	1065	218 (20.5)	693 (65.1)	76 (7.1)	78 (7.3)
Active	58	11 (18.9)	37 (63.8)	5 (8.6)	5 (8.6)
All					
Inactive	5453	873 (16.0)	3715 (68.1)	358 (6.6)	507 (9.3)
Active	433	71 (16.4)	255 (58.9)	42 (9.7)	65 (15.0)
ICDAS $_{3+4}$					
Molars					
Inactive	299	14 (4.7)	94 (31.4)	148 (49.5)	43 (14.4)
Active	176	10 (5.7)	36 (20.5)	75 (42.6)	55 (31.3)
Premolars					
Inactive	60	9 (15)	12 (20)	25 (41.7)	14 (23.3)
Active	32	2 (6.3)	3 (9.4)	13 (40.6)	14 (43.8)
Anterior					
Inactive	46	9 (19.6)	7 (15.2)	21 (45.7)	9 (19.6)
Active	59	6 (10.2)	11 (18.6)	27 (45.8)	15 (25.4)
All					
Inactive	405	32 (7.9)	113 (27.9)	194 (47.9)	66 (16.3)
Active	267	18 (6.7)	50 (18.7)	115 (43.1)	84 (31.5)

3.2.5. Multilevel Poisson regression analysis

In the first model, after adjustment for co-variates and confounding factors, we found that micro-cavitated/shadowed lesions (ICDAS $_{3+4}$) were 1.39 times more likely to progress than non-cavitated lesions (ICDAS $_{1+2}$) within two years follow up. In the second model where lesions' severity and activity at the baseline was considered, after adjustments for confounding factors, we found that active non-cavitated and active micro-cavitated/shadow lesions had 1.78 and 1.96 times higher rates to progress respectively compared to non-cavitated inactive lesions. Only inactive micro-cavitated/shadowed lesions (ICDAS $_{3+4}$) did not show higher rate of progression compared to inactive non-cavitated lesions. Regarding the surface type, we found that pits and fissures had 1.36 times higher rates of caries progression compared to the smooth surface lesions. The proximal lesions had 1.56 times higher rates of caries progression compared to the smooth surface lesions. However, the CIs for pits and fissures and proximal surfaces effect estimates are overlapping. Regarding tooth type, molars and premolars had 1.44 and 1.33 times higher rates of caries progression respectively compared to anterior teeth. However, the CIs for molars and premolar effect size estimates are overlapping (Table 7).

Table 7: Multilevel Poisson regression analysis of the 2-years primary caries lesions progression rate in Belarusian adults based on lesions' baseline severity and activity status, the surface, and the tooth type.

Exposure Variables	Crude Rate Ratio, 95% CI	Adjusted Rate Ratio, 95% CI
First level: Surface		
***Lesion Severity status** (ref. ICDAS $_{1+2}$)		
ICDAS $_{3+4}$	1.42 (1.18, 1.71)	1.39 (1.16, 1.67)
**** Lesion Activity/Severity status** (ref. ICDAS $_{1+2}$, inactive)		
ICDAS $_{1+2}$, active	1.65 (1.32, 2.06)	1.78 (1.40, 2.24)
ICDAS $_{3+4}$, inactive	1.07 (0.80, 1.43)	1.06 (0.79, 1.42)
ICDAS $_{3+4}$, active	2.01 (1.57, 2.56)	1.96 (1.53, 2.51)
Surface type (ref. smooth)		
Pits& fissures	1.28 (1.06, 1.56)	1.36 (1.11, 1.66)
Proximal	1.41 (1.18, 1.69)	1.56 (1.29, 1.87)
Second level: Tooth		
Tooth type (ref. anterior)		
Molar	1.33 (1.10, 1.61)	1.44 (1.18, 1.76)
Premolar	1.28 (1.02, 1.59)	1.33 (1.06, 1.66)

*For the first model our exposure variable was primary lesion severity status at the baseline only, not taking into account lesion's activity. The model was adjusted for age, gender and baseline caries experience (D_{1-6}, active). Tooth and surface type were treated as covariates.

**For the second model our exposure variables were primary lesions severity/activity status at the baseline, tooth and surface types. The model was adjusted for age, gender, and baseline caries experience (D_{1-6}, active).

4. Comprehensive scholarly discussion of all the findings

In this study, we assessed the extent to which caries lesions' severity and activity status are associated with caries lesion progression in adults. In addition, we investigated how the tooth and tooth surface types are associated with caries lesion progression. The study results have shown that in caries active adults: 1) active caries lesions were more likely to progress to more severe conditions than inactive lesions; moreover, the progression of active lesions to more severe conditions or becoming cavitated, restored, or missing is two times more likely than with inactive lesions regardless of lesion severity stage (non-cavitated or micro-cavitated/shadows). 2) The likelihood of progression of inactive micro-cavitated/shadow lesions was almost the same as for non-cavitated inactive lesions. 3) When focusing only on baseline caries severity status, tooth surfaces with micro-cavitated/shadow caries lesions had a higher progression rate to more severe conditions compared with non-cavitated caries lesions.

Our findings of the high likelihood of caries progression in tooth surfaces with active caries lesions compared to inactive lesions agreed with previous studies conducted in children with the use of ICDAS criteria that showed that caries lesions diagnosed as active presented a higher risk to progress than inactive lesions (Ferreira Zandoná et al., 2012; Guedes et al., 2014) within 2-4 years follow up. In our study, the RR for ICDAS $_{1+2}$ active and ICDAS $_{3+4}$ active progression was quite close, with overlapping CIs of 95%. However, for example, in a cohort study assessed caries lesion progression among children using ICDAS diagnostic systems over 48 months together with yearly bitewing radiographs (Ferreira Zandoná et al., 2012), they stated that caries progression depended on the severity and activity of the lesions.

Our findings of the high likelihood of caries progression in tooth surfaces with greater baseline caries severity agreed with previous studies (Ferreira Zandoná et al., 2012; Guedes et al., 2014; Ismail et al., 2009; Ismail et al., 2015; Milsom et al., 2008) that were conducted among children using the ICDAS criteria. Guedes and coworkers conducted two years cohort study among children aged 12 to 59 months old, they reported that the relative risk of progressing of surfaces with $ICDAS_2$ and $ICDAS_3$ was 1.98 (CI, 95% 1.25, 3.14) and 6.28 (CI, 95% 3.79, 10.39) respectively compared to surfaces with $ICDAS_1$ (Guedes et al., 2014). In another two years cohort study (Ismail et al., 2015) conducted among children aged 0-5 years old, it was stated that 1. surfaces with baseline $ICDAS_{1\ \&\ 2}$ scores were 9.6 times more likely to progress to $ICDAS_{3\ \&\ 4}$ at follow-up than sound surfaces (RR = 9.6, 95% [CI = 7.0– 13.1]); 2. the rate ratio (RR) of caries progressing from baseline initial caries $ICDAS_{1\ \&2}$ to extensive caries $ICDAS_{5\&\ 6}$ was 6.1 (95% CI = 4.7-7.9) compared to sound surfaces; 3. surfaces with baseline moderate caries $ICDAS_{3\ \&4}$ had 20.6 times the rate of caries progressing to extensive caries compared to sound surfaces (95% CI = 16.4-25.9).

Moreover, Ferreira Zandoná and coworkers found that caries progression to cavitation varied by surface type, baseline caries severity, and activity status (Ferreira Zandoná et al., 2012). In our study, pits and fissures, and proximal surfaces showed a greater likelihood of caries progression than smooth surfaces while adjusted to age, lesion severity and activity status, which agreed with aforementioned study and other existing evidence (Batchelor & Sheiham, 2004; Broffitt et al., 2013; Warren et al., 2006).

In a cross-sectional study conducted among Australian volunteers, it was reported that the prevalence of proximal caries in posterior teeth was the highest in the 36-51 years age group compared to younger age groups (17-20, 21-25, 26-30, and 31-35 years) (Hopcraft & Morgan, 2006). The higher progression of caries lesions on proximal surfaces in our study compared with anterior teeth can be explained by: 1.the age group: about 80% of the participants were at the age group 35-54 or 55 and older; 2. plaque control on proximal surfaces is more difficult than on smooth surfaces, which are more cleansable (Fejerskov, 2004); 3. According to the self-administered questionnaire data, most of our participants did not use dental floss regularly. The lower caries progression rate on smooth surfaces in our population compared with occlusal or proximal surfaces may be explained by better circumstances for plaque control and better exposure to saliva and fluoride products. Our results were confirmed in a previous study conducted by (Broffitt et al., 2013; Ferreira Zandoná et al., 2012; Guedes et al., 2014).

Our findings showed that the likelihood of caries lesions progression in posterior teeth was higher than in anterior teeth, with minimal difference between molars and premolars. This corroborates the previous study conducted among children aged 5-13 years to assess caries lesion progression in permanent teeth and reported that molars are more liable to have caries lesions followed by premolars and anterior; also, caries lesions located on molars showed the most significant progression rate, followed by premolars, while anterior lesions showed the lowest progression (Ferreira Zandoná et al., 2012). In a birth cohort study conducted in New Zealand from the age of 5 to the age of 38 years old, it was reported that the highest caries experience was found in molars and premolars, and the lowest caries experience was in the anterior teeth (Broadbent et al., 2013).

Our self-administered questionnaire data have shown that most of our study participants were low educational level workers with low monthly income of ≤300$. Most participants (83.1%) reported using fluoridated toothpaste, and 33.7 % of the participants reported visiting the dentist in the last

12 months for regular check-ups. At the same time, most of our study participants had at least one active non-cavitated or cavitated caries lesion at the baseline. It was previously reported that low income was associated with high dental caries severity (Costa et al., 2013) and poorer oral health status. A systematic review conducted by Costa and coworkers reported that worse socioeconomic status (education, income, occupation) was associated with a greater severity of dental caries in adults (Costa et al., 2012). Moreover, it was stated that the widening of the social gradient of caries disease with age also confirms the requirement for dental public health improvement modalities to address the social determinants of dental problems (Hall-Scullin et al., 2017).

Not only in Belarus but worldwide, few longitudinal studies have been conducted in adults aged ≤60 years due to difficulties in maintaining follow-up (Broadbent et al., 2013; Chaffee et al., 2015; Dobloug & Grytten, 2015; Sugihara et al., 2014). The most important limitation of this study was the loss of follow-up that exceeded 20% of the sample (34.9%). In our study the participants at baseline and follow-up were similar regarding sociodemographic and oral health behavioural characteristics except for the age. We found that most of people dropping out were from younger group (18-34 years), which makes sense as young adults are always searching for new jobs to improve their income. At the same time, this may affect our effect size estimate by underestimating our findings related to caries progression rates since the dropped-out group had a higher average number of active non-cavitated and cavitated caries lesions compared to the follow up group of the same age. Additional data analysis strategies should be implemented (e.g., multiple imputation approach) to assess how the loss to follow-up affected the two-years caries lesions progression rates in the study population.

The results of our study generated from adults with high caries activity levels and thus may be extrapolated only to caries active adults' population. In addition, one may argue that utilizing the same examiner for the baseline and follow-up examinations should account for its limitations as the examiner was aware that most adults were caries active at the beginning of the study. We acknowledge this limitation; however, the examiner was blinded to the baseline data. Additionally, the reliability of caries diagnosis according to lesion severity and activity showed substantial agreement according to the grading scale for the interpretation of kappa values (Landis & Koch, 1977). We need to acknowledge that in this study, caries lesions detection on dentinal level for proximal surfaces might not be completely accurate as there were no additional detection methods used (e.g., radiographic examination; teeth separation). However, it was reported that the summary sensitivity estimates were highest for visual-tactile methods (ICDAS, the Ekstrand-Ricketts-Kidd, and the Nyvad systems) (0.83, CI 0.77- 0.87), while radiographic imaging had the lowest sensitivity (0.50, CI 0.40 - 0.59) (Walsh et al., 2022). Thus, using robust and detailed visual or visual-tactile diagnostic criteria permits achieving a high level of sensitivity for proximal surfaces caries detection (Walsh et al., 2022).

Alongside these limitations, this study also has several strengths: it is a prospective cohort study in adults on caries progression where clinical examinations were performed based on tooth surface level using contemporary caries diagnostic criteria that permit assessing caries lesion severity and activity status. To our knowledge, there is no published article focusing on the same research question in the current scientific literature in adults' population. Moreover, the intra-examiner reliability was appropriate, which increases the precision of the results. We used a multilevel Poisson regression model to control for confounding variables and take in to account the nesting effect of our data (individual, surface, tooth). In this regression model, the effect of the variable of interest can be assessed with confounding variables held constant statistically (Wang & Kattan,

2020) since the confounding variables may lead to over/underestimation or even inverse the direction of an effect (Vakorin et al., 2009).

Implications

Our findings showed that precise detection and assessment of dental teeth surfaces by the ICDAS system, for assessment of caries lesions' severity, combined with the Nyvad system, for assessment of caries lesions' activity provided an essential information for appropriate caries management planning and linked with different patterns of caries lesions progression. We found that caries lesions progression in adults depends on lesion severity and activity status, tooth and surface type. Therefore, it is crucial to inform dentists about the importance of contemporary diagnostic criteria to be utilized in everyday practice. Moreover, caries lesion severity and activity assessment can be a precious tool for clinicians to utilize to opt for management decisions and surface prognosis. Careful monitoring and non-surgical management of initial active caries lesions can minimize surgical intervention, leading to improved clinical outcomes. Furthermore, our findings provided additional key evidence concerning caries lesion progression in adults, which is lacking when contemporary visual-tactile diagnostic criteria are used.

5. Conclusion

In our study of a caries active adult population in Belarus which was examined using the ICDAS and the Nyvad criteria, after two years of follow-up, we found that more severe lesions were more likely to progress than less severe lesions; and active caries lesions were more likely to progress to more severe conditions than inactive lesions. Also, regardless of their severity, inactive lesions had a lower rate of progression than active lesions. More longitudinal studies focusing on caries lesions progression in adults using contemporary caries diagnostic systems with longer follow-up period and robust methodology are needed.

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7. APPENDICES

Appendix 1. Description of International Caries Detection and Assessment System (Ismail, 2007)

ICDAS severity codes

Code	Description
0	Sound
1	First Visual Change in Enamel (seen only after prolonged air drying or restricted to within the confines of a pit or fissure)
2	Distinct Visual Change in Enamel
3	Localized Enamel Breakdown (without clinical visual signs of dentinal involvement)
4	Underlying Dark Shadow from Dentin
5	Distinct Cavity with Visible Dentin
6	Extensive Distinct Cavity with Visible Dentin

ICDAS restorative codes

0 = Sound: i.e. surface not restored or sealed (use with the codes for primary caries)

1 = Sealant, partial

2 = Sealant, full

3 = Tooth colored restoration

4 = Amalgam restoration

5 = Stainless steel crown

6 = Porcelain or gold or PFM crown or veneer

7 = Lost or broken restoration

8 = Temporary restoration

9 = Used for the following conditions

96 = Tooth surface cannot be examined: surface excluded

97 = Tooth missing because of caries (tooth surfaces was coded 97)

98 = Tooth missing for reasons other than caries (all tooth surfaces were coded 98)

99 = Unerupted (tooth surfaces coded 99)

Appendix 2. **<u>Nyvad codes (B. Nyvad et al., 1999)</u>**

ICDAS score	Clinical Characteristics of Caries Lesion (Nyvad criteria)	
	Active=1	Inactive=0
ICDAS 1-4	Surface of enamel is whitish/yellowish opaque with loss of luster; feels rough when the tip of the probe is moved gently across the surface; lesion is in a plaque stagnation area	Surface of enamel is whitish, brownish, or black; enamel may be shiny and feels hard and smooth when the tip of the probe is moved gently across the surface
ICDAS 5-6	Cavity feels soft or leathery on gently probing the dentine	Cavity may be shiny and feels hard on gently probing the dentine