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## Remarkable decline and sustained low levels of caries in the Nordic populations — Explanations and implications for public oral health

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### Abstract

Community water fluoridation has been acclaimed as an effective mode of caries control at the population level. However, a recent review has concluded that in high-income populations with widespread access to topical fluorides, water fluoridation (0.7 ppm F) has a minor effect on the development of caries. It may therefore be relevant to take a historical look at the benefits of an oral health intervention that does not rely on the use of systemic fluorides, such as toothbrushing with fluoride toothpaste. We summarize the evidence from large population studies in the Nordic countries during the past 50-yr and show that it is possible to obtain and sustain low caries levels over decades by self-performed use of fluoride toothpaste. Topical fluoride at low concentrations *treats/arrests* active/progressing caries lesions by controlling mineral loss in dental hard tissues, thereby reducing the development of cavities. Toothbrushing with fluoride toothpaste shifts the entire caries distribution to the left, including the right-hand tail end of the distribution, ensuring that also the more disadvantaged groups may benefit. Daily brushing with fluoride toothpaste should be promoted and trained through school-based oral health programs for children. It is time for a reappraisal of fluoride toothpaste for public oral health.

### INTRODUCTION

Recently, we have experienced the revival of an old debate whether systemic fluoride is

necessary to obtain a maximum caries reduction in populations. This dispute was most likely initiated by the US Secretary of Health, RF Kennedy Jr., after he announced that community water fluoridation should be discontinued to avoid—in his view—an unnecessary risk of neurotoxic health [1]. We do not intend to add to the debate about possible neurotoxic effects but would like to point out that increased ingestion of fluoride during tooth formation, irrespective of the source, will add to the risk of increasing prevalence and severity of dental fluorosis indicative of a toxicological effect on mineralization [2].

The continued endorsement during the past 70-yr of the use of systemic fluoride as the preferred cost-effective caries prevention stems predominantly from the USA and the UK/Commonwealth association. The possibility of targeting the entire population irrespective of socio-economic differences [3] has been a key argument for this mode of administration of fluoride. The introduction of water fluoridation was less successful in Europe and many other countries. To mimic the systemic effect of water fluoride, some countries introduced caries preventive programs using fluoride tablets, fluoridated salt, or fluoridated milk. Unlike water fluoridation, these measures are associated with compliance issues, which may serve to increase inequalities in oral health.

The promotion of fluoridated toothpaste, which had previously been considered less effective than water fluoridation, was stimulated by a critical evaluation of observations from epidemiological, chemical, and clinical studies suggesting that the major cariostatic effect of fluoride is topical rather than systemic [4]. Increased use of self-applied fluoride via toothpaste occurred in parallel with a caries decline, particularly in the Nordic countries during the 1980's and 1990's. Owing to population-based registries, we know that this decline has continued for more than 50-yr, and the prevalence of caries at cavitation level among 12-yr-old children is now, according to WHO, among the lowest in the world [5]. It is important to try to understand the role of topical fluorides in this development.

Recently, a systematic review and a large epidemiological study have indicated that the effects on caries progression of having fluoride in the drinking water might be smaller than estimated before the widespread use of fluoride toothpaste [6, 7]. This observation is particularly thought-provoking in view of the persistent promotion of water fluoridation by dental associations [8, 9]. The obvious question is therefore whether we still need water fluoridation for population control of dental caries.

In this focus article, we aim to share our reflections about the benefits and potential drawbacks of the current most used strategies for caries prevention: community water fluoridation and self-applied brushing with fluoride toothpaste, with particular emphasis on the long-term impact on dental caries of regular use of fluoride toothpaste in the Nordic populations.

## WHAT IS AT STAKE FOR WATER FLUORIDATION

For more than 70-yr community water fluoridation has been appraised for its effectiveness to reduce dental caries, and still “health authorities consider it a key strategy for preventing dental caries” [6]. A systematic review from 2000 covering studies published in the period 1959–2000 concluded that water fluoridation had resulted in a caries prevalence, which was 14.6% (IQR = 5.1%–22.1%) lower in fluoridated areas than in non-fluoridated areas, and a DMFT value that was 2.25 lower in fluoridated than in non-fluoridated areas [10]. A subsequent Cochrane review found a reduction in DMFT of 1.16 (95% CI = 0.72–1.61) as a result of the initiation of water fluoridation [11]. However, because most of the studies in the review [11] were conducted prior to 1975, it was unclear whether the results were relevant in the context of the current widespread use of topical fluoride products, including fluoride toothpaste, varnishes, gels, and rinses. Moreover, the authors estimated that about 12% of the children living in areas with a fluoride level as low as 0.7 ppm F in the water supplies experienced dental fluorosis of aesthetic concern and 40% had fluorosis of any level [11]. Dental fluorosis reflects a toxicological effect of the total daily fluoride intake on enamel formation, irrespective of the source [12].

The observations above were confirmed in a recent Cochrane review in which meta-analyses were stratified as to whether data were collected before or after 1975 [6]. It was thus apparent that the benefits on caries progression of having fluoride in the water supplies were smaller than estimated before the common exposure to fluoride in toothpaste and other topical fluoride interventions [6] and possibly even clinically unimportant [7]. Furthermore, the recent studies found no convincing evidence that water fluoridation reduces social inequalities in caries [6, 7], even though this previously has been a significant argument for establishing water fluoridation programs in many countries [13].

Legal and ethical aspects of fluoride applications have seldom been addressed in relation to public oral health strategies [5]. This is particularly problematic for community water fluoridation, by which large groups of people may be obliged to drink fluoridated water against their will without being informed about potential adverse health effects [14], including the increased risk of dental fluorosis [12]. For these reasons, Veneri *et al.* [14] have referred to community water fluoridation as a form of “mass medication” [15]. Although such an approach might in some countries have been tolerated in the 1960s and 1970s at a time when dental caries prevalence was extremely high, the caries prevalence in most industrialized countries is now so low that violation of individual rights to medical self-determination, ignoring potential adverse effects of fluorides, can no longer be accepted.

## EARLY EXPERIENCES WITH FLUORIDE TOOTHPASTE IN

## DENMARK

The severe caries situation in Denmark after the Second World War prompted a decision to introduce special caries prevention programs for children. In a small, relatively rich community north of Copenhagen, a preventive program aimed at oral health education for parents, but this intervention did not markedly change the caries prevalence in permanent teeth of 8-yr old children over 4-yr [16]. However, after the introduction of fluoride toothpaste in 1964, a more elaborate pilot program in the same community comprising various caries preventive measures at school, such as intensified oral health education for parents and children, monthly toothbrushing instruction and exercises, and fortnightly mouth rinsing with 0.2% NaF solution, showed remarkable results. Together with the common use of fluoride toothpaste, this program led to a 30% caries reduction during the following 3–4-yr [16, 17]. The effect of the program was primarily ascribed to an effect of fluoride [17], but it could not be excluded that factors such as improved living conditions, increased level of education, and/or changes in diagnostic and treatment criteria had played a role for the continued decline [16, 17]. Nevertheless, despite persistent success of the program, supervised mouth rinsing with fluoride solution was withdrawn because the effect was found to be negligible [18], presumably because fluoride toothpaste was used for home care [19]. In a neighboring community, prescription of fluoride tablets was withdrawn because they gave rise to dental fluorosis [20].

The elaborate preventive programs discussed above were not representative of the entire country; many children in less populated areas did not have access to free community dental clinics and were served by private dentists. But gradually, over a decade, most children became exposed to preventive programs, including topical fluorides. Although the programs varied between communities, the key component was always fluoride toothpaste.

In 1972, the health authorities in Denmark introduced legislation about free oral health care for all school children, a law that was gradually expanded to include preschool children as well. This approach came with compulsory annual recordings of the caries status of each child and has resulted in a unique database that provides strong evidence for how dental caries has developed for more than half a century. Hence, a paper presented at the first international conference on caries decline held in Boston in 1981 confirmed that a caries decline had taken place in Denmark during the 1970s and that it was indeed possible to reduce the development of caries at the population level without using systemic fluorides [21].

Concurrently with the introduction of fluoride toothpaste in the Nordic countries, periodontology grew as a separate research discipline with its own departments at dental schools all over Scandinavia. In particular, the experimental gingivitis studies conducted by Löe *et al.* [22] resulted in an extensive focus on toothbrushing for the prevention of periodontal diseases. This approach was implemented in private and public dental clinics and may, as a

positive side effect, have driven a rapid increase in the use of fluoride toothpaste.

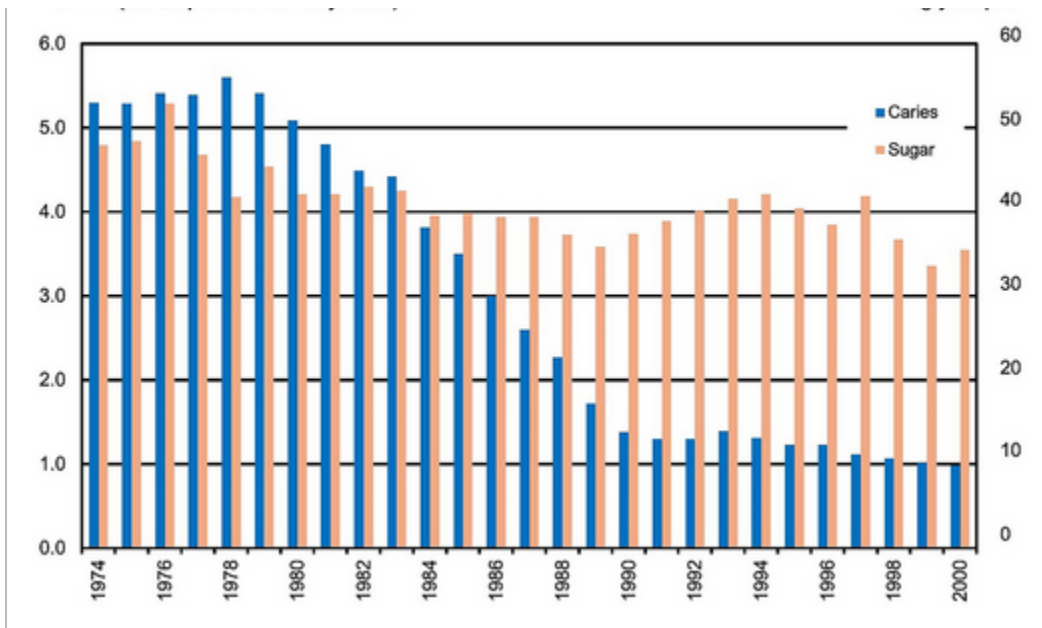
## THE CARIES DECLINE IN THE NORDIC COUNTRIES

The caries decline became apparent over a relatively short period of 20-yr in all the Nordic countries at the end of the last century [23-27]. During this period, the mean caries experience was typically reduced from about 6–7 to 1–2 DMFT in 12-yr-old children, whereas the proportion of “caries-free” children increased from 5% to about 50% [28]. In Iceland, the steepest part of the decline occurred concurrently with an increase in the volume of fluoridated toothpaste sold [23], which supports the assumption that fluoride in the toothpaste might be part of the explanation for the decline.

The low caries levels in the Nordic countries have continued to decrease into the 21st century, although at a slower rate. Norwegian researchers analyzed changes of caries in five birth cohorts (age range 14–72) during the period 2003–2012 using longitudinal data collected annually over a period of 10-yr and found that the mean number of carious teeth per patient decreased in all birth cohorts [27]. Importantly, nearly 90% of the patients had no new caries lesions for 5-yr, and 50% had no new caries lesions for 8-yr, irrespective of the birth cohort. Correspondingly, a recent longitudinal study of caries in cohorts of Danish children and adults has shown a steady and continued improvement of the dental status over the past decades, implying that good dental health in childhood continues into adulthood [29].

It may come as a surprise that the caries decline occurred in parallel with continued high sugar consumption in all the Nordic countries of around 40 kg/capita/yr (Figure 1) [28-30], and in Iceland, up to 50 kg/yr. This counters the widely held view that there is a positive relationship between the amount of sugar consumed and dental caries [31]. However, the evidence for this relationship is mainly based on population studies conducted prior to the introduction of fluoride toothpaste, and a study of sugar consumption in 90 developing and industrialized countries from the 1990's reported that the sugar–caries relationship was less clear [32]. Although 28% of the variation in DMFT for the whole data set could be explained by sugar consumption, a separate analysis of data for the industrialized countries showed that less than 1% of the variation was accounted for by sugar intake [32]. This suggests that when fluoride is used regularly in combination with tooth brushing, the sugar consumption–caries relationship has weakened and may have a lower impact on caries development [33]. Among other factors, it may be speculated that reduced plaque levels facilitated by toothbrushing [34] increases the penetration of fluoride through dental biofilm, thus improving its effect on active caries processes [35]. This does not mean, however, that reduction of sugar consumption is no longer beneficial for general health.

	DMFT (caries prevalence 12-yr-olds)	Kg/yr/capita
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**FIGURE 1**

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Sugar consumption (kg/yr/capita) in Denmark and caries prevalence (DMFT) in 12-yr-old Danish school children from 1974 to 2000. Data from the Danish Health Authority [28] and Dansukker [30].

The fluoride concentration of the natural drinking water in the Nordic countries is generally low, typically in the order of 0.1–0.5 ppm F. A Danish study concluded that even very low levels of fluoride (0.125–0.25 ppm F) in the drinking water could play a role in reducing caries risk [36]. Unfortunately, the authors seem to have ignored the daily fluoride exposure added by toothbrushing. This represents an inherent problem in analytical studies of the effect of multiple fluoride sources. Hence, the regular exposure to fluoride from toothpaste may have added considerably to the total fluoride exposure beyond that obtained from drinking water alone.

## SCHOOL-BASED TOOTHBRUSHING REVISITED

Because the use of fluoride toothpaste combines two crucial caries preventive measures—an effect of oral hygiene and a fluoride effect—it is not possible to perform a rigorous clinical trial comparing the effect of fluoride in toothpaste versus the effect of community water fluoridation. However, epidemiological studies have shown that children living in a non-fluoridated community in Ireland using fluoride toothpaste as basic caries prevention experienced larger reductions in the proportion of cavitated caries lesions than children living in a contemporary fluoridated district (0.6–0.8 ppm F) [37]. This suggests that the success of fluoride in caries control may not just be a question about fluoride exposure, but that plaque

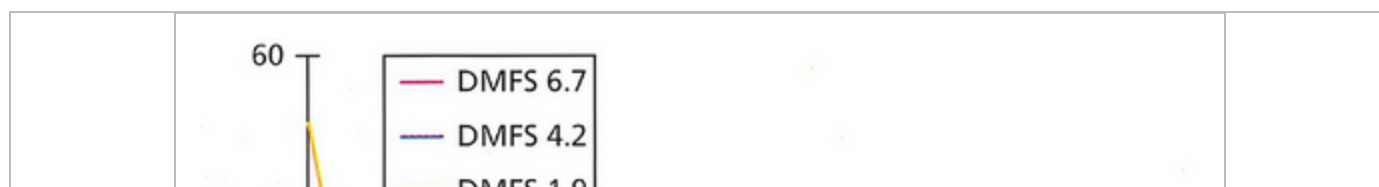
removal—disturbance of the cariogenic environment in the dental biofilm—by means of toothbrushing could also play a significant role.

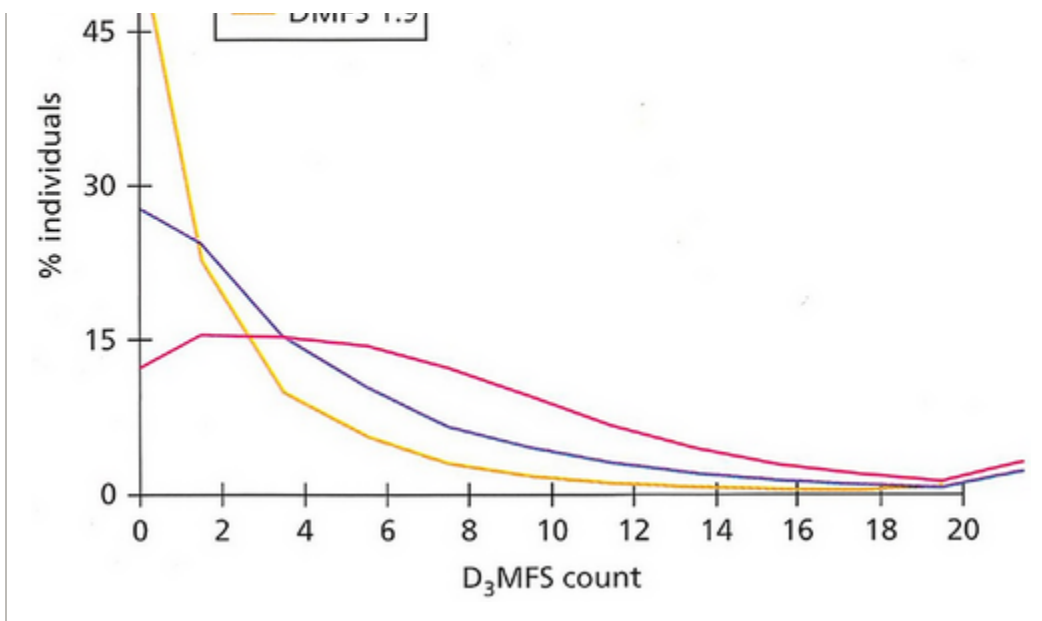
Oral health interventions at the individual level have often been miscredited because they may only show temporary improvements in patients' knowledge and behavior [38]. However, recent systematic reviews of clinical trials covering countries in Asia, Europe, Africa, and America have concluded that school-based oral health promotion programs for children can have long-term positive impacts on plaque accumulation, gingivitis, and caries [39, 40]. According to these reviews, the success of such programs relies on practical training in toothbrushing, in addition to support and guidance from parents, teachers, and/or dental personnel [39]. Indeed, caries preventive programs combining education in oral health and training in toothbrushing or daily supervised toothbrushing with fluoride toothpaste at school have shown that caries progression in high-caries children can be reduced to about one half within 2.5–3-yr [34, 41]. Simultaneously, the proportion of tooth surfaces covered by visible plaque may be reduced from approximately 70% to 11% [34].

There is no specific protocol or mix of personnel required to obtain the desired goal [39]; what matters is the dedication and knowledge of the supervising personnel to teach and motivate groups of children to brush their teeth with fluoride toothpaste. Toothbrushing is easy to implement in schools everywhere in the world and does not require advanced dental equipment. Toothbrushing should therefore become a behavioral norm on par with general hygiene.

## CHANGES IN THE DISTRIBUTION OF CARIES BECAUSE OF THE CARIES DECLINE

Significant changes in the frequency distribution of individuals were observed when mean  $D_3MFS$  counts in cohorts of 15-yr-old Danish children were plotted according to decreasing caries levels in 1988 ( $D_3MFS = 6.7$ ), 1993 ( $D_3MFS = 4.2$ ), and 2012 ( $D_3MFS = 1.9$ ), respectively (Figure 2) [42]. The graphs clearly illustrate that a lower mean  $D_3MFS$  is associated with a change across the whole population, with markedly more individuals with very little disease and a lower fraction with very high levels of disease. Indeed, such shifts in the caries distribution imply that a caries preventive approach based on toothbrushing with fluoride toothpaste fulfills the classical characteristics of a population strategy, as defined by Rose [43] and discussed by Watt [44].



**FIGURE 2**

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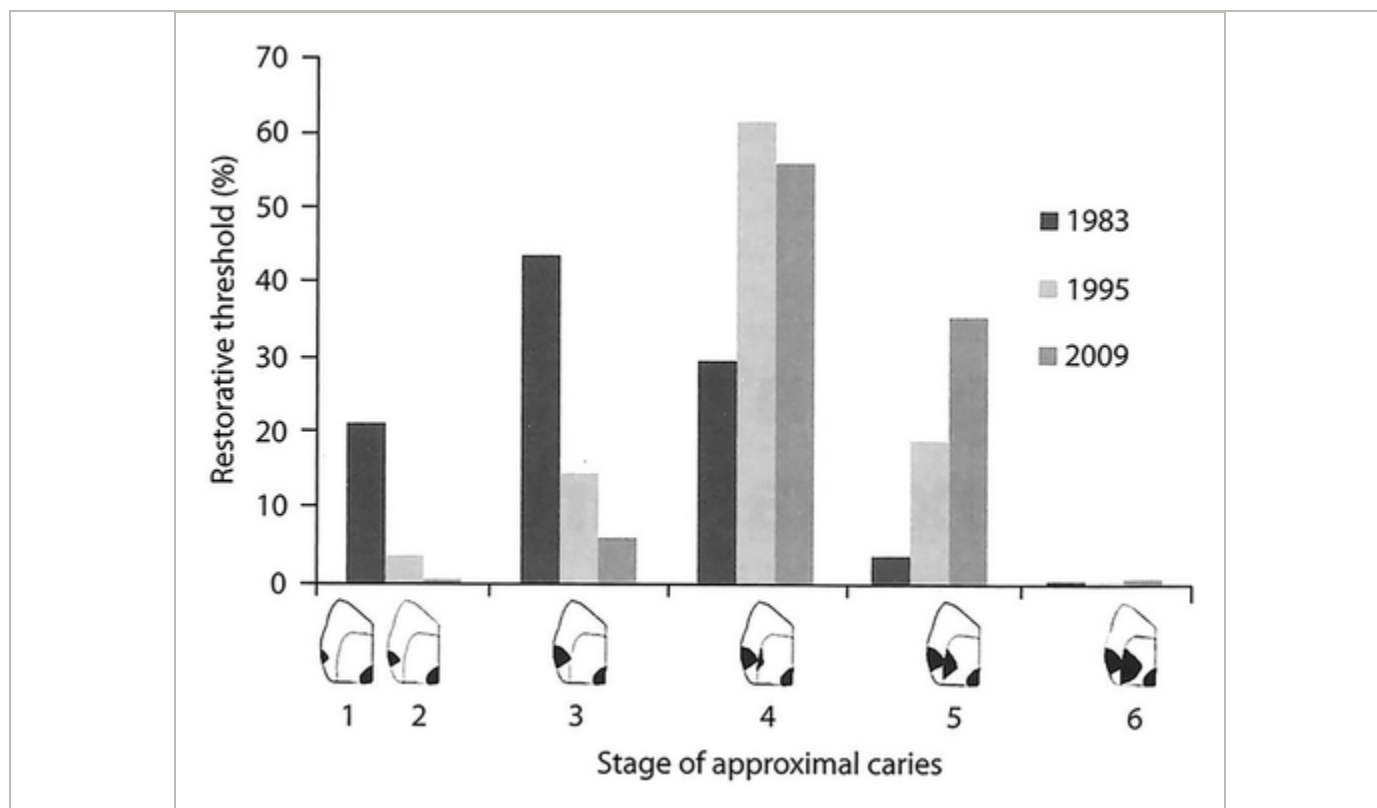
The frequency distribution of individuals according to their individual  $D_3MFS$  counts as the mean  $D_3MFS$  for the population decreases. Data from the Danish public dental health service for 15-yr-olds in the yrs 1988, 1993, and 2012 [28]; [42] (reproduced with permission from *Wiley Blackwell*).

The steep rise in the proportion of “caries-free” individuals because of the caries decline may at first glance look as if the population strategy is more beneficial for the healthier part of the population (Figure 2). However, this is most likely a result of differential uptake of health-conducive preventive behaviors, which, in turn, may be influenced by numerous characteristics at the individual, community, and societal levels [45]. Such changes in the distribution of caries indicate that some individuals more readily adopt or become more skilled in performing plaque removal than others. Inevitably, when caries preventive programs are introduced, the “low-hanging fruits” are the first to be picked, and it is probable that the most severely affected groups will need upstream or special targeted community interventions and/or financial disincentives addressing remaining inequalities [46].

## ROLE OF DENTISTRY IN THE CARIES DECLINE

It has often been ignored that dentists’ decisions about operative treatment of caries can have a marked influence on the caries prevalence in populations. In this regard it should be appreciated that shifts in the timing of operative interventions of caries may have contributed significantly to the caries decline in the Nordic populations. The lower rate of caries lesion progression called for nonoperative intervention, and dental practitioners were therefore

advised to adopt a nonoperative approach for the management of non-cavitated lesions and to postpone operative intervention until the stage of clinically visible cavity formation [47]. Although many practitioners were initially concerned about abstaining from restoring clinically intact approximal lesions with radiolucency in inner enamel and outer dentin, the concept turned out to be successful without causing long-term adverse effects. Hence, it was estimated that the risk for an approximal caries lesion being filled decreased to only one fifth over a 7-yr period in Danish adolescents from 1978 to 1985 [48]. Similarly, Norwegian practitioners extended the threshold for restorative intervention to progressively deeper stages of lesion development into the dentin during the period of the caries decline [49] (Figure 3). The important lesson from these observations is that if patients should benefit from the lower rate of caries progression, treatment decisions based solely on dental radiographs must be abandoned. Caries lesion activity and cavity formation cannot be detected reliably on dental radiographs, and too much reliance on radiography leads to overtreatment of non-cavitated caries lesions [50].



**FIGURE 3**

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Restorative threshold for approximal caries lesions based on pictograms illustrating different radiographic stages of caries progression in 1983, 1995, and 2009. The pictograms (1–6) indicate stages of approximal caries used to determine respondents' criteria for initiation of restorative treatment. 1: Lesion extending into outer half of enamel. 2:

Lesion extending between outer half and two-thirds into enamel. 3: lesion extending to dentin–enamel junction. 4: Lesion extending into outer third of dentin. 5: Lesion extending no more than two thirds into dentin. 6: Lesion extending into inner third of dentin [49] (reproduced with permission from *Caries Res*).

As expected, the above changes in treatment recommendations enabled a gradual move from restorative management of caries to a focus on self-care and disease control in the Nordic countries.

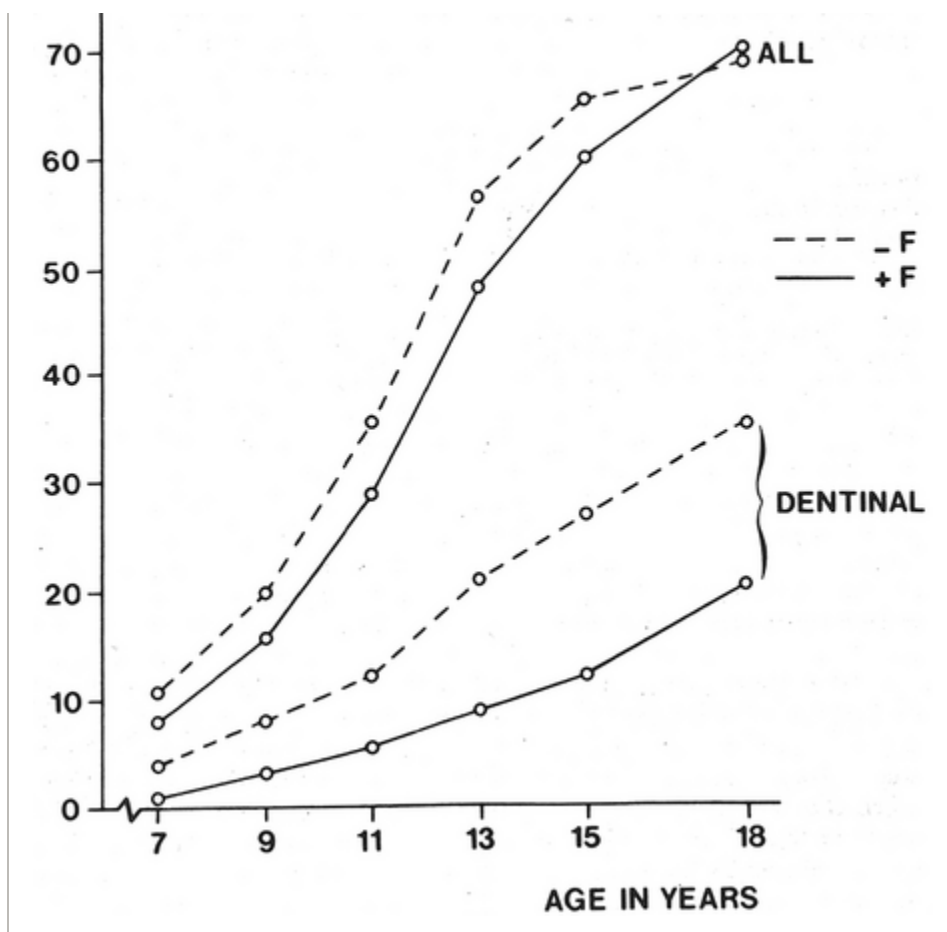
## TOPICAL FLUORIDE IS A THERAPY THAT CONTROLS LESION DEVELOPMENT AT ALL STAGES OF DENTAL CARIES

All tooth surfaces are at risk of caries because of continuous metabolic processes in the dental biofilm under normal physiological conditions [51, 52]. These metabolic processes result in dynamic pH fluctuations in the dental biofilm environment and explain why dental caries is a chronic condition that requires lifelong control in all populations.

Fluoride is a remedy that interferes with these processes. Every time the pH in the dental biofilm fluid becomes undersaturated with respect to hydroxyapatite, tooth mineral starts to dissolve from the hard dental tissue. However, if fluoride ions are available in the biofilm environment simultaneously, the biofilm fluid may be supersaturated with respect to fluorhydroxyapatite at pH intervals in the pH range 4.8–5.5, and the mineral loss can be controlled by precipitation of fluoridated apatite in the surface layer of the caries lesions [53], whereas dissolution of hydroxyapatite may continue deep to the surface. The net outcome of these processes is a slowing down of the rate of caries lesion progression when fluoride is present in the local environment. *This explains the therapeutic effect of fluoride.*

Fluoride does not *prevent* the development of caries lesions. Reanalysis of a Dutch longitudinal study on the effect of water fluoridation showed that when enamel lesions were included in the caries recordings, fluoridated drinking water had hardly any effect on the total number of cavitated and non-cavitated caries lesions in children compared to a control group not exposed to fluoridated water [54] (Figure 4). The fluoride effect was ascribed to a much lower proportion of cavities in the fluoride group. Collectively, these observations support the hypothesis that fluoride is a therapeutic remedy that *treats ongoing caries processes by controlling the rate of development of carious cavities.*

	ALL SURFACES	
N		



**FIGURE 4**

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Total number of lesions—enamel and dentin—and number of dentin lesions developing in all tooth surfaces in children participating in a longitudinal study of the effect of water fluoridation from 7 to 18-yr of age. The number of all lesions on approximal surfaces was calculated from standardized bitewing radiographs [54] (reproduced with permission from *Community Dent Oral Epidemiol*).

Some researchers and clinicians may consider the discussion about fluoride as a therapy rather than prevention as a question about semantics. However, it is important that patients understand that they themselves can modify the rate of caries lesion development by regular disturbance of the dental biofilm with a fluoride-containing toothpaste through which fluoride ions interact with the ever ongoing mineral dissolution processes. Fluoride slows down the rate of dissolution of minerals when present in the biofilm fluid. Thus, fluoride has a therapeutic effect every time pH fluctuations occur during ongoing caries processes.

## ACTIVE LESIONS NEED ACTIVE INTERVENTION WITH FLUORIDE

As it may be difficult for the clinician to identify those non-cavitated caries lesions that benefit from topical fluoride treatment, Nyvad *et al.* developed a clinical diagnostic system that can be used to monitor the activity of non-cavitated caries lesions over time [55]. When the criteria were validated in a clinical trial of the effect of daily supervised brushing with fluoride toothpaste, it was shown that the criteria reflected the caries-controlling effect of fluoride: that is, active lesions benefited more from fluoride toothpaste than inactive lesions [56]. Moreover, predictive validity showed that active non-cavitated lesions were at higher risk of progressing to the cavity/filled state than were inactive non-cavitated lesions [56]. Clinical caries lesion activity assessment therefore provides dental practitioners with an evidence-based diagnostic tool for the detection of lesions in need of intensified caries control with fluoride [57]. Inactive lesions, most of which may remain inactive for a lifetime, do not require further intervention.

Caries lesion activity assessment has also shown its value as a screening tool for the identification of caries-active individuals in low-caries populations. This was explored in a randomized clinical trial in teenagers in Finland in which patients with one or more active non-cavitated lesions were subjected to a nonoperative program comprising individually designed preventive interventions [58]. At the end of the 4-yr trial, the prevented fraction of DMFS was 44% lower in the test group than in the control group receiving standard basic prevention offered in the public dental clinics [58]. The caries reduction was remarkable because a previous nonoperative intervention using a risk approach for allocation of patients into a high-risk group did not show a significant effect on caries increments [59]. This suggests that caries lesion activity assessment may circumvent the problem of the low accuracy of caries risk assessment [60]. Thus, Batchelor and Sheiham [61] concluded that in a study of caries lesions developing over a 4-yr period, most new lesions occurred in children classified at lowest caries risk at baseline, whereas children classified as high risk at baseline contributed less than 6% of the total number of new lesions.

## CONCLUDING REMARKS AND RECOMMENDATIONS

In this paper, we have shown that it has been possible to reduce caries levels in the Nordic child populations from being among the highest in the world to being among the lowest and to sustain such low levels of caries for half a century by means of a public oral health program largely based on self-applied brushing with fluoride toothpaste. These changes have occurred despite continued high levels of sugar consumption. Concurrently with the caries decline, the entire caries distribution in the population shifted to the left, including the most caries affected individuals at the right-hand tail end of the distribution, resulting in a significant reduction in the overall levels of disease. Collectively, these observations indicate that toothbrushing with fluoride toothpaste is a robust population strategy that should be promoted as a valid alternative to community water fluoridation for the control of dental caries.

Brushing with fluoride toothpaste is basic caries control for rich and poor. It treats and controls active caries processes as caries lesions develop. Toothbrushing in groups avoids victim-blaming and promotes the development of toothbrushing as a social norm. Some epidemiologists might contend that for theoretical reasons it may be more appropriate to solve the caries problem by restricting sugar consumption [44]. We do not disagree with this theoretical reasoning, but so far, we have not seen any evidence in literature demonstrating that dietary interventions might be helpful in reducing dental caries or other noncommunicable diseases in contemporary populations. Similarly, lowering the sugar intake by a 20% volumetric tax on sugar-sweetened beverages has indicated only a modest caries reduction of 2%–3% in children over a 10-yr period [62].

It is often assumed that preventive programs based on toothbrushing with fluoride toothpaste may be particularly successful in countries with high social welfare and access to modern dental clinics. However, as discussed in this paper, toothbrushing habits are best introduced and trained in groups of children in school environments supported by parents, teachers, or dental personnel. In its very basic form, the only necessary equipment needed, in addition to toothbrushes and toothpaste, is access to a water tap. Many cavitated lesions may not progress rapidly when controlled by proper toothbrushing, especially in the primary dentition [63, 64]. Alternatively, cavitated lesions that are difficult to clean may be handled nonoperatively by atraumatic restorative techniques (ARTs) [65]. Toothbrushing can therefore be recommended as a strategy in any setting where local community health care workers can easily be trained to promote oral health at primary schools.

The *chronic* nature of dental caries implies that carious processes can never be eliminated; however, they can be controlled. A recent health economic analysis from the United Kingdom has indicated that with today's low levels of caries, it is questionable whether community water fluoridation may offer a cost-effective alternative to caries preventive programs based on topical fluorides, including brushing with fluoride toothpaste [7]. Cessation of water fluoridation has shown that caries levels are likely to increase [66, 67] if exposure to water fluoride is not replaced by alternative topical fluoride strategies, such as fluoride toothpaste. Toothbrushing with fluoride toothpaste is a highly cost-effective public health intervention for caries [68] and should be made accessible and affordable to individuals and populations all over the world. The Nordic experience shows that once toothbrushing has been taught and trained from early childhood, this habit develops into a social norm that passes down from one generation to the next.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Bente Nyvad and Ole Fejerskov. **Writing—original draft:** Bente Nyvad.

**Writing—critical review and editing:** Bente Nyvad and Ole Fejerskov.

# CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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