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BRIEF RESEARCH REPORT
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Relationship Between Dental Caries and Erosive Tooth Wear in Adolescents

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Background: Our aim was to investigate the relationship between caries experience and erosive tooth wear in adolescents.

Methods: We compared the Decayed, Missing, and Filled Teeth (dmft/DMFT) data of 795 adolescents to their erosive tooth wear scores using diet as a covariate and determined whether dental caries and erosive tooth wear scores are associated with each other, using linear regression analysis. Diet data and oral hygiene habits were collected using self-reported surveys and erosive tooth wear scores were previously collected. We also compared patients' genotypes and phenotypes and looked for an association between erosive tooth wear experience and different single nucleotide polymorphisms (SNPs). A Bonferroni correction was implemented to correct multiple comparisons. Two-group comparisons were made depending on the phenotype definitions implemented, and both chi-square and linear regression analyses were used to the test association between genetic variants and caries definitions. All covariates were included in each model.

Results: For four SNPs (rs17159702, rs10246939, rs1800972, and rs1676303), there was an association between a spike in caries experience of DMFT 4 or more between two time points and increased frequency of fruit juice intake. A fifth SNP rs2860216 was shown to be a protective factor against a caries spike when associated with more frequent yogurt consumption. We did not find significant associations between our dental caries phenotypes or our demographic data and erosive tooth wear status in our linear regression.

Conclusions: Dental caries and erosive tooth wear are two diseases that differ in mechanism and heritability.

Keywords: dental caries, dental erosion, genetics, adolescent and youth, association studies in genetics

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INTRODUCTION

Erosive tooth wear is caused by acid from food and drink, stomach acid due to vomiting or reflux, occupational exposure and so on, or is idiopathic (1). Soft drinks, juice, and fruits are culprits of erosive tooth wear, especially in younger patients (1–6). A genome-wide association study (GWAS) had suggested a genetic influence on the condition (7). An association between enamel formation genes and erosive tooth wear was reported previously (8, 9).

In our previous work, we found that eating sour sweets and drinking acidic beverages (specifically sports drinks) are associated with dental erosive wear in the population, while tooth brushing frequency was not (5). This study was followed by the demonstration that *amelogenin* and *enamelin* were associated with having erosive tooth wear (8). Since it was suggested that some genes involved in enamel formation were associated with dental caries and also associated with erosive tooth wear, here we expanded this inquiry to additional genes (8–10). Our hypothesis is that dental caries and erosive tooth wear may be modulated by similar genes. The genetic variants elected to be studied here were shown to be linked to dental caries.

In this report, we tested whether associations could be detected when dental caries phenotypes based on longitudinal data (10) were associated with having erosive tooth wear and certain dietary habits.

TABLE 1 | Groups created in the previous study based on dmft/DMFT scores.

Group	Sample size, *n*
No caries (DMFT = 0) vs. low caries (DMFT ≤ 3)	201 vs. 301
No caries vs. high caries (DMFT ≥ 4)	201 vs. 373
Low caries vs. high caries	301 vs. 373
No primary caries (dmft = 0) vs. low primary caries (dmft ≤ 3)	647 vs. 125
No primary caries (dmft) vs. high primary caries (dmft ≥ 4)	647 vs. 103
Low primary caries (dmft) vs. high primary caries (dmft)	125 vs. 103
No caries vs. very high caries (DMFT ≥ 8)	201 vs. 128
Very high caries vs. low caries	301 vs. 128
Very high caries vs. high caries	245 vs. 128
Acute increase in DMFT (DMFT increased by 4 or more between time points) vs. no acute increase in DMFT	128 vs. 527
Acute increase in DMFT vs. no caries	128 vs. 201

MATERIALS AND METHODS

Of 846 adolescents from Western Norway (aged 16–18 years) scheduled for dental recall examinations, 795 (94%) agreed to participate (10, 11). This project was approved by the Regionale Komiteer for Medisink og Helsefaglig Forskningsetikk—REK (approval number 2011/1602) and the University of Pittsburgh Institutional Review Board (IRB) (approval number 12110620). Written informed consent was obtained from all participants and/or their parents. These patients were broken down into groups based on longitudinal analysis of their Decayed, Missing, and Filled Teeth (DMFT/dmft) scores and genotyped to determine if there are certain host genetic factors that associate with dental caries experience. Patients were unrelated, healthy, and had regular access to dental care. Caries experience ($D_{3-5}MFT/d_{3-5}mft$) data were obtained from the patients' dental records and collected as part of a routine dental examination. Concerning approximal lesions recorded during the radiographic examination, only dentin lesions were included (D/d_{3-5}). DMFT/dmft scores were recorded at different ages, and depending on the birth year of participants, they had 4, 5, or were DMFT scores overtime. Dentists treating these children were calibrated by the same professional, but no intra-examiner reliability scores were obtained.

These groups created based on the patients' DMFT/dmft are listed in **Table 1**.

Each DMFT/dmft was collected at a different time point depending on the patient's birth year. DMFT/dmft scores were recorded at different ages, and depending on the birth year of participants, they had 4, 5, or 6 DMFT scores overtime. Children born in 1994 had DMFT/dmft data recorded at ages 5, 12, 14, 16, 17, and 18. Children born in 1995 had DMFT/dmft data recorded at ages 5, 12, 14, 16, and 17. Finally, children born in 1996 had DMFT/dmft data recorded at ages 5, 12, 14, and 16. Individuals with low caries experience included subjects with a DMFT score of 1, 2, or 3, and individuals with a high caries experience included subjects with a DMFT score of 4 or more. We chose our high caries DMFT/dmft score as 4 or more due to the mean DMFT/dmft score for the population being 3.5. Patients from the high caries experience group were split into a high caries group with a DMFT score of 4 or more and a very high caries group with a DMFT score of 8 or more. Eight was chosen as the DMFT cutoff since it is double the number used for high caries experience. We also separated patients based on whether or not they had an acute increase in caries experience between two time points. We called these acute increases "spikes" for short and looked to see if patients experienced more than one spike over time. In total, 128 patients had a spike of four or more between two time points, while the next most common spike was five and occurred in only 42 patients. Therefore, a spike was defined as an increase in a DMFT score of 4 or more between two time points based on our previous determination of high caries experience and based on the distribution of increases between time points across the population.

In this study, the same patient group genotyping results found in previous studies were compared to additional variables, such as diet and oral hygiene behaviors and erosive tooth wear scores. Patients were given self-administered questionnaires to completely describe their oral hygiene and dietary habits at the time the last DMFT score was obtained (5). Prior to initiating the study, the questionnaire was completed by a pilot group ($n = 10$) to ensure comprehension and legibility (5). The survey included questions about brushing, beverage and food consumption, workout habits, and acid regurgitation frequency. A complete list of questions and possible responses are part of the **Supplemental Materials**.

Some questions had a low frequency of differing responses and were not included in the following analysis. Those included are listed in **Table 2**. Responses were given scores to be included in the analysis and are also listed in **Table 2**.

In recall examinations, dental erosive wear for 795 patients of the Norwegian cohort was determined using the Visual Dental erosion Dental Examination scoring system (5, 12). Eight calibrated dentists and hygienists collected erosive tooth wear data. Calibrations were performed through the use of photographs and coaching by the same professional. Twenty surfaces of 14 teeth were selected as index surfaces: the occlusal surfaces of the upper and lower first and second molars and

the labial and palatal surfaces of the upper incisors and canines. Patients with ≥3 index surfaces with dental erosive wear were defined as affected (5). Additional descriptive information on calibration and collection of erosive tooth wear data can be found in previous work (8, 11, 12). Intraexaminer agreement (kappa) was 0.77, with the initial loss of enamel looking to be the most challenging to be scored.

Genotyping was obtained using TaqMan chemistry (13) (Applied Biosystems genotyping probes and master mix, Waltham, MA, USA) and end-point analysis in a 7900HT Fast Real-Time PCR system with a 384-well block module (Applied Biosystems, Waltham, MA, USA). Saliva samples were obtained using DNA Genotek's saliva-based collection kits (Ottawa, ON, Canada), and DNA was extracted weeks later at the time of genotyping according to the protocol of the manufacturer.

TABLE 2 | Covariates included in each linear regression test.

Covariate (questions from survey)	Responses and scoring for analysis
Sex	Male = 1, Female = 2
Last dental visit	0–6 months = 1, 7–12 months = 2, 13–24 months = 3, more than 24 months = 4
How often the patient brushes teeth	"Rarely" = 1, "Once daily" = 2, "Twice daily" = 3, "More than twice daily" = 4
How long the patient brushes teeth	"Less than 2 min" = 1, "Between 2 and 5 min" = 2
Is a supplemental fluoride source used?	"Rarely or never" = 1 "Once weekly" = 2 "2–3 times per week" = 3, "Daily" = 4
Frequency of juice intake	"Rarely or less than one time per week" = 1, "1–2 times per week" = 2, "3–5 times per week" = 3, "once daily" = 4, and "more than once daily" = 5.
Frequency of soda/diet soda intake	
Frequency of sports drink intake	
Frequency of eating citrus fruits	
Frequency of eating apples	
Frequency of eating chips with dip	
Frequency of eating yogurt	
Frequency of eating acidic sweets	
Erosion (3 or more affected surfaces)	Affected = 1, Unaffected = 2

A linear regression was performed using the PLINK software (14) to look for an association between chosen habits, which are listed in **Table 2**, and erosive tooth wear, single nucleotide polymorphisms (SNPs) that were genotyped, and our newly created dental caries phenotypes from a previous study are listed in **Table 1** (10).

In addition, the PLINK software was used to compare patients' genotypes and phenotypes and look for an association between erosive tooth wear experience and the different SNPs from our previous study (10). A Bonferroni correction was implemented to correct for multiple comparisons. Two-group comparisons were made depending on the phenotype definitions implemented, and both chi-square and linear regression analyses were used to test for the association between genetic variants and caries definitions. All covariates were included in each model. A flowchart of the steps executed in the methodology is presented in **Figure 1**.

RESULTS

A number of SNPs were found to show an association with the covariates as compared to dental caries experience. These are listed in **Table 3**. Due to the number of p below 0.05, this table includes only nominal results with $p < 0.01$ and the results that hold significant after a Bonferroni correction where the association was set at $p = 0.001$ (0.05/49). The results significant after Bonferroni are in bold.

No significant associations were found between the erosive tooth wear phenotype and SNPs from genotyping studies.

DISCUSSION

This study aimed to demonstrate that similar biological factors of the host could be implicated in dental caries and erosive

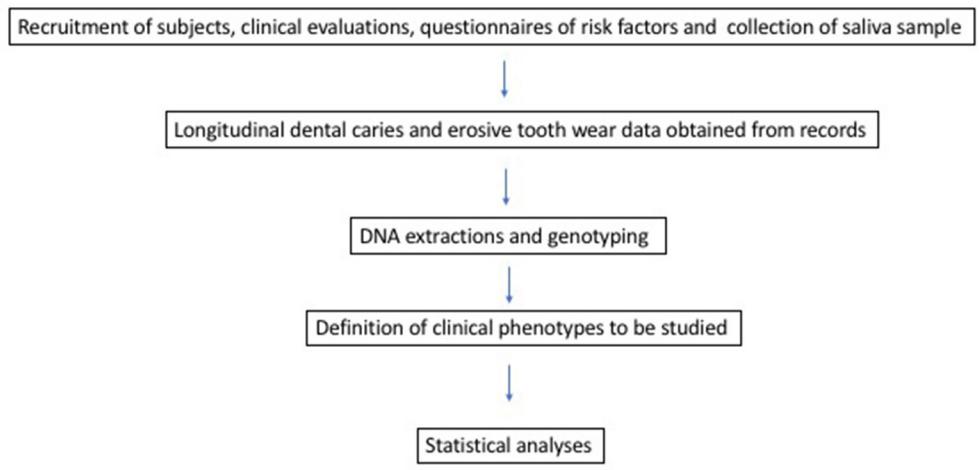

FIGURE 1 | Summary of study design.

TABLE 3 | Summary of the association analysis.

Phenotypic comparison	Chromosome	SNP	A1	Covariate	*N*	*p*-value
No primary vs. high primary	12	rs461872	A	Supplemental fluoride	157	0.009
	12	rs467323	A	Chips and dip	305	0.004
	12	rs3736309	G	Supplemental fluoride	593	0.009
	14	rs10132091	C	Erosion	675	0.009
Very high caries vs. no caries	4	rs4694075	T	Diet soda frequency	244	0.004
	5	rs375129	T	Diet soda frequency	272	0.005
	5	rs27565	A	Diet soda frequency	187	0.002
	7	rs10246939	C	Diet soda frequency	285	0.007
	12	rs296763	C	Diet soda frequency	307	0.01
	14	rs8011979	T	Diet soda frequency	275	0.009
	14	rs2860216	C	Diet soda frequency	278	0.01
	17	rs7217186	C	Soda frequency	92	0.006
	22	rs5997096	T	Diet soda frequency	237	0.004
Very high caries vs. low caries	5	rs375129	T	Diet soda frequency	343	0.007
	5	rs27565	A	Diet soda frequency	226	0.008
	7	rs17159702	C	ADD	403	0.01
	12	rs461872	A	Supplemental fluoride	88	0.004
	14	rs7150049	G	Diet soda frequency	383	0.005
	14	rs1676303	C	Diet soda frequency	386	0.01
Very high caries vs. high caries	14	rs8011979	T	ADD	300	0.005
Spike vs. no caries	4	rs4694075	T	Diet soda frequency	255	0.01
	22	rs5997096	T	Diet soda frequency	249	0.008
Spike vs. caries	1	rs9701796	G	Frequency of juice	647	0.003
	4	rs4694075	T	Eating yogurt	520	0.009
	5	rs375129	T	Frequency of juice	538	0.009
	5	rs27565	A	Frequency of juice	356	0.009
	5	rs6862039	A	Frequency of juice	563	0.003
				Eating yogurt		0.005
	7	rs17159702	C	Frequency of juice	638	**0.0006**
	7	rs10246939	C	Frequency of juice	567	**0.0008**
	7	rs1726866	T	Frequency of juice	600	0.006
	8	rs1800972	C	Frequency of juice	298	**0.0002**
	12	rs2878771	C	Frequency of juice	645	0.002
			C	Eating yogurt		0.008
	12	rs3736309	G	Frequency of juice	537	0.002
				Eating yogurt		0.01
	12	rs296763	C	Frequency of juice	635	0.003
	12	rs1996315	G	Frequency of juice	660	0.003
				Eating yogurt		0.007
	14	rs1997532	C	Frequency of juice	616	0.001
				Eating yogurt		0.007
	14	rs1997533	C	Frequency of juice	483	0.006
				Eating yogurt		0.003
	14	rs7150049	G	Frequency of juice	589	0.007
	14	rs8011979	T	Frequency of juice	556	0.01
	14	rs4903399	T	Frequency of juice	604	0.007
				Eating yogurt		0.004
	14	rs6574293	A	Frequency of juice	580	0.004
Spike vs. caries	14	rs10132091	C	Frequency of juice	604	0.002
				Eating yogurt		0.01
	14	rs1077430	A	Frequency of juice	531	0.004

(Continued)

TABLE 3 | Continued

Phenotypic comparison	Chromosome	SNP	A1	Covariate	*N*	*p*-value
	14	rs745011	C	Frequency of juice	581	0.003
				Eating yogurt		0.008
	14	rs1676303	C	Frequency of juice	615	**0.0005**
				Eating yogurt		0.002
	14	rs2860216	C	Frequency of juice	568	0.005
				Eating yogurt		**0.0009**
	17	rs2619112	A	Frequency of juice	601	0.005
	19	rs2235091	C	Frequency of juice	613	0.002
				Eating yogurt		0.002
	19	rs198968	A	Frequency of juice	550	0.006
Spike vs. caries	14	rs10132091	C	Frequency of juice	604	0.002
				Eating yogurt		0.01
	14	rs1077430	A	Frequency of juice	531	0.004
	14	rs745011	C	Frequency of juice	581	0.003
				Eating yogurt		0.008

The values given in bold indicate Bonferroni-corrected significant values.

tooth wear. We attempted to carry out a careful clinical characterization to utilize novel phenotypes for the study of dental caries and erosive tooth wear. After a Bonferroni correction, five results stood out as significant. All of these results were included in the comparison of the groups "acute increase vs. caries." In our previous study, we separated patients based on whether or not they had an acute increase in caries experience (between any two time points) of a DMFT score of 4 or more (10). For four SNPs (rs17159702, rs10246939, rs1800972, and rs1676303), there was an association between a spike in the caries experience of a DMFT score of 4 or more between two time points and an increased frequency of fruit juice intake. SNP rs17159702 is found in aquaporin 1 (*AQP1*) and therefore may have a role in salivary buffering and dental caries (15). SNP rs10246939 is found in taste 2 receptor member 38 (*TAS2R38),* which may indicate an association between taste preferences and juice intake (16). SNP rs1800972 is found in defensin beta 1 (*DEFB1*), an inflammatory response gene (17, 18). Finally, SNP rs1676303 is found to flank estrogen-related receptor beta (*ESRRB*), which may have a developmental role in a patient's dentition (19).

Intake of juices is reported as a major covariate for dental caries and erosive tooth wear. Studies have shown previously that increased juice intake leads to increased early childhood caries (20, 21). Other studies have contradicted this, finding that increased consumption of fruit juice leads to lower instances of dental caries in children (20). However, studies like this one speculate that children who drink less juice may have more dental caries because they are substituting juice with more cariogenic drinks (19). Not as much data are available for adults and the frequency of dental caries in those who drink juice as compared to those who do not. To our knowledge, this is the first study that has looked at the impact of drinking more juice on a subset of patients with an acute increase in dental caries experience between two time points. Therefore, while other studies have not necessarily shown an association between increased juice intake and increased caries experience, studies such as this one have only examined overall caries experience and not longitudinal data.

Dairy intake is also suggested as a risk modulator of dental caries and erosive tooth wear. A fifth SNP rs2860216 was shown to be a protective factor against a caries spike when associated with more frequent yogurt consumption. This SNP lies in *ESRRB* and has also been shown to play a potential role in caries experience as a gene involved in dental development (19). In previous studies, eating yogurt has been found to potentially hamper the effects of *Streptococcus mutans* due to its probiotic nature and lower the risk for dental caries (22–24). Again, to our knowledge, this is the first study to show the potential protective role of yogurt consumption in patients who may otherwise experience a spike in dental caries.

Another modulator of risk is soda intake. Very high caries experience (DMFT $\geq$ 8) vs. no caries seems to be borderline-associated with increased diet soda intake. This seems counterintuitive, since diet soda usually has sugar removed. Studies have agreed that soda causes a demineralization of the tooth structure and that artificially sweetened soda intake yields less dental caries than full-sugar soda. However, studies have shown that artificially sweetened sodas still have some cariogenic potential (25). Patients may also be drinking more artificially sweetened sodas because they believe they are healthier than regular sodas. This may account for the extra high caries experience in some patients compared to those with no caries.

Diets high in sugar and carbohydrates have been known to play a role in dental caries experience. The Vipeholm studies were some of the earliest studies demonstrating this (26). While erosive tooth wear and dental caries differ in their causation, they are both mediated by diet and therefore the dietary survey responses can be applied to dental caries experience as well (1). We were limited in our dietary analysis because we did not have longitudinal diet data. Data were collected at one point

in time when the patients were either 16, 17, or 18 years of age. Therefore, it was a bit of a stretch to analyze our primary caries groups with our diet data since they were collected when the patients had only permanent dentition. However, because the patients still live at home and are relatively healthy in their habits, the diets may still reflect those that impacted the primary dentition. Moreover, there are gaps in time between when the caries data were collected and when the diet data were collected. However, by stratifying our patients into groups based on their trends in caries experience rather than caries experience at certain time points, we believe that the diet data are still relevant.

However, there were several limitations in this study. Because the questionnaires were self-administered, the results may be affected by recall bias or selective reporting by patients. Additionally, while the DMFT/dmft data were longitudinal, the diet data were collected at one time point between the patient ages of 16 and 18. Therefore, there is no information on past dietary preferences or tooth brushing habits (5). However, there was a 94% response rate for patients across the entire questionnaire and therefore the likelihood of non-response bias is low (5).

For future work, as research of the genetic influences on erosive tooth wear is limited, a GWAS could be indicated as well for that disease. Also, there are additional diet data that we did not analyze in our linear regression. Specifically, the methods of drinking fluids (from glass, bottles, sports bottles, or straws) were not analyzed in this study as they were beyond its scope. They were, however, analyzed in the previous studies of erosive tooth wear (5), where consumption of diet soft drinks from a glass or straw resulted in a significantly lower prevalence of dental erosive wear compared to drinking from a bottle. For the other acidic beverages, no significant associations were found when comparing the chosen drinking method and erosive tooth wear. It may be an interesting pursuit to determine whether the methods of drinking acidic or cariogenic beverages (i.e., through a straw and swishing in the mouth) affect dental caries experience. Additionally, our study concludes that dental caries and erosive tooth wear are two diseases that differ in mechanism and heritability. This study may provide insight into the heritability of erosive tooth wear, and despite both dental caries and erosive tooth wear being disease conditions that stem from demineralization of the hard tissues of teeth, they are, in fact, different from each other.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, and further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Pittsburgh Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MW and AV conceived and planned the experiments. MW carried out the experiments and took the lead in writing the manuscript. JS, AMu, KD, and AT contributed to sample preparation. MW, AMo, and AV contributed to the interpretation of the results. All authors provided critical feedback and helped to shape the research, analysis, and manuscript. These data are part of a thesis of MW submitted as part of the requirements to the fulfilment of a Ph.D. in Oral Biology.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdmed.2021.738443/full#supplementary-material

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