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CLINICAL REPORT

# Interventional Three-year Longitudinal Study of Melanocytic Naevus Development in Pre-school Children in Dresden, Saxony

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**Acquired melanocytic naevi (MN) are considered a risk factor for melanoma. Exposure to ultraviolet light (UV) is the major environmental factor for MN. UV protection is most critical in pre-school children. This 3-year interventional longitudinal study examined 395 3-year-old children attending daycare centres (DCC) in Dresden, Germany. Photo-skin type, eye and hair colour were recorded. DCC were randomly assigned to a control group and a behavioural intervention group. All children had a regular naevus check-up, including digital objective analysis with Dell'Eva-Burroni Dermoscopy Melanoma Image Processing Software (DB-MIPS) technology. Parents of children in the intervention group received additional guidance for sun-protection. The mean total MN counts of both groups at the start of the study period were 7.19 ± 4.55 (intervention) and 6.84 ± 4.63 (control), respectively. There was a significant increase in MN counts for both groups (mean 12.5 and 13.8). Subgroup analysis for skin type, eye colour, and hair colour did not demonstrate a significant influence on MN counts. The DB-MIPS integrated classifier revealed no risky lesions while analysing their patterns. Intervention did not reduce the number of newly acquired MN. MN counts in pre-school children were approximately 5 times higher than expected from previous large studies in Germany. This is the first study in pre-school children using objective digital image analysis of pigmented lesions. No atypical lesions were observed. New approaches to UV protection in pre-school children are now required.** ***Key words: melanocytic naevus; UV-light exposure; pre-school children; primary prevention; objective image analysis.***

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Acquired melanocytic naevi (MN) are considered a major risk factor for cutaneous melanoma (CM) (1). Whereas the total MN count has a strong genetic background, as demonstrated by twin studies in subjects with fair skin complexion (2, 3), the increase in MN counts reflects UV exposure and interaction between environment and skin (4–7). Increase in MN count is a surrogate marker for UV exposure (8).

There is a general consensus that UV exposure during childhood is most critical to determine the future risk of CM (9–19). Protective measures, such as UV-absorbing or reflecting textiles and seeking shadow in the middle of the day, reduce UV exposure. The use of sunscreens for UV protection is still under debate, since controversial results have been obtained in clinical trials. Several studies have observed an increased MN count in sunscreen users during childhood (20–26). In contrast, one study on adults suggests regular sunscreen use may prevent primary CM (27).

We conducted a prospective randomized controlled trial in pre-school children. The dynamics of MN counts were evaluated by objective digital imaging of MN. Regular education of parents was investigated as a possible tool in the primary prevention of acquired MN and compared with a control group.

## MATERIALS AND METHODS

The study was planned as a randomized prospective controlled trial over a period of 3 years (2009 to 2012), starting with the youngest children at the age of 3 years in the daycare centre (DCC). The study was approved by the ethics committee of the Saxonian Physicians Chamber, Dresden, Germany.

A total of 14 DCC participated in the study. Children in the control group received standard care plus regular MN check-ups including objective digital imaging. Parents with their children in the intervention group received additional guidance about sun-protection and had regular parent meetings with a dermatologist twice a year. Printed material was handed out. Parents were informed about the possible harmful effects of sun/UV exposure, about UV-index, textile UV-protection, sunscreens and sun-protective behaviour. After obtaining informed consent from parents the inclusion rate in the different DCC was between 21% and 95%. A final total of 395 children, aged 3 years, was enrolled.

### *Setting*

Dresden is the capital of Saxony, located in the South-East of Germany, latitude 51°05' N and longitude 13°74' E.

### *Skin examination*

Whole-body skin examinations and photography were carried out every year throughout the study (T1 – first year, T2 – second year, and T3 –final year) by 2 experienced dermatologists (CH and AB). Data were collected on MN distribution and size, skin

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pigmentation, hair and eyes, tanning and freckling, and Fitzpatrick photo-skin type (28). Eye colour was classified into blue, green, brown, and black. Hair colour was classified as blonde, red, brown, and black. Skin phototype was not a selective criterion for this trial. Parents were asked about sunburn in their children.

*Melanocytic naevi*

A standard protocol was used to evaluate MN (29). MN were defined as hyperpigmented papules or plaques (brown or black), darker than the surrounding skin, irrespective of their diameter. Freckles, solar lentigines and café-au-lait spots were excluded based on clinical criteria. Locations of MN were marked on an anatomical chart for 18 different anatomical regions.

*Digital dermoscopic analysis of melanocytic lesions*

For objective analysis of MN the DB-MIPS mobile analyser for skin cancer prevention (BioMIPS Engineering srl, Siena, Italy) was used. The DB-MIPS system is based on a handily polarized microscope and is able to show real-time process and store high-resolution images of skin lesions. Each lesion is grabbed at a horizontal view of 16 mm. The lesions are stored through a proper database together with the patient's data. The DB-MIPS system evaluates 49 variables of geometrics, colour, colour distribution and texture. Lesion identification is realized by clustering (30–32).

*Statistics*

DCC were selected randomly from all available institutions in order to prevent systematic mistakes by preferring city districts and social groups. DCC were cluster randomized to the interventional or control groups. This resulted in 7 DCC for each group, with 248 (interventional) and 257 (control) children. Definition of criteria for randomization and randomization itself was realized by SAS software SAMPLE2 and SAS procedure RANUNI (random number from a continuous uniform distribution). Sample-size planning was based on 90% power for detection of difference of acquired MN during 3 years' follow-up using the data of Wiecker et al. (2). We expected a 20% reduction in MN count in the intervention group. However, the results show that the basis of the sample-size planning has not been sufficient and a cluster effect has not been included. In 2-sided *t*-tests *p*-values $< 0.05$ were considered significant.

The total body count of MN was the primary outcome variable in this study. It was evaluated by linear models of covariance analysis using the factors "group" (i.e. interventional or control) in 2 independent categories and the factor "time" in 3 correlated categories (i.e. T1, T2, T3) assuming compound symmetry for the residual covariances within each DCC and heterogeneity between the random DCC to take cluster effects into consideration. Subsequent Tukey-adjusted multiple comparisons of means between groups and time-points were performed. In a second variant we used the MN number at T1 as a covariable to adjust the group comparison.

To evaluate the skewness of the distribution of MN counts in descriptive analysis, distribution was characterized by median, means, standard deviations, and box-plots. Empirical distribution of MN counts showed sufficient symmetry for parametric statistical inferences. Subgroup analysis used the 2-sided *t*-test for null hypothesis. Throughout this study statistical software SAS (http://support.sas.com/documentation/) was employed.

## RESULTS

A total of 395 children participated in this study. Compliance was high (97%). Total MN count of both groups (interventional and control) at T1 was $7.19 \pm 4.55$ (mean ± standard deviation (SD)) and $6.84 \pm 4.63$, respectively (Fig. 1, Table I). Our data show a significant increase in MN counts for both groups at T2 and T3 compared with T1 (Table SI[1]). The MN count of T3 is not the sum of T1 and T2, since some MN obviously disappeared.

A subgroup analysis was performed for clinical covariants. In our study, gender was not associated with statistically significant differences in MN counts. Most children belonged to skin type 2 ($n = 316$). There was a non-significant tendency to more acquired MN in children of skin type 2 and 3 compared with skin type 1. Blue and brown were the most frequent eye colours. Eye colour had no significant influence on MN counts (Fig. S1[1]). The dominant hair colour was blonde. Hair colour had no significant influence on MN counts (Fig. S2[1]). The body areas with the highest MN counts were the face, posterior trunk, and anterior lower arms (Tables SI[1] and SII[1]).

The mean size of MN increased significantly from T1 to T2 and from T1 to T3 for both groups ($p < 0.0001$) (Table II). The mean size of all newly developed MN at T3 was 1.48 mm. There was no significant difference between the 2 groups. The percentage of naevi with a diameter ≥2 mm decreased from T1 to T3 from $13.45 \pm 18.29$ (control) and $13.38 \pm 16.35$ (intervention) to $7.34 \pm 6.39$ and $8.12 \pm 6.33$, respectively. This is due to the development of new small MN and the disappearance of some larger MN.

The DB-MIPS integrated classifier (30) revealed no risky lesions while analysing their patterns. Signs of atypical lesions among the DP-MIPS variables (31), such as asymmetry of shape and colour distribution, regression and increase in entropy were absent, and the resulting mean score of all lesions in both groups was practically zero, translating into completely benign lesions.

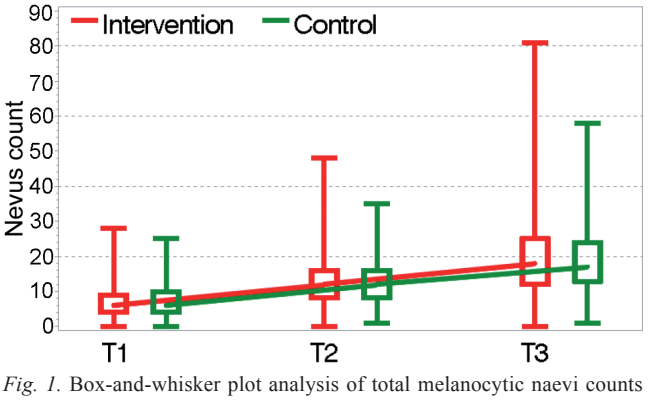


*Fig. 1.* Box-and-whisker plot analysis of total melanocytic naevi counts of pre-school children ($n = 395$) during the first (T1), second (T2), and third year (T3) of investigation. *Boxes*: 25th and 75th percentiles; *whiskers*: minimum and maximum values of the distributions; *bold lines*: means.

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Table I. *Comparison of melanocytic naevi (MN) counts*

| Contrast | *p*-value rough | *p*-value Tukey-adjusted |
|---|---|---|
| Intervention vs. control | 0.6936 | 0.6936 |
| T1 vs. T2 | <0.0001 | <0.0001 |
| T2 vs. T3 | <0.0001 | <0.0001 |
| T1 vs. T3 | <0.0001 | <0.0001 |
| Intervention T1 vs. T2 | <0.0001 | <0.0001 |
| Intervention T2 vs. T3 | <0.0001 | <0.0001 |
| Control T1 vs. T2 | <0.0001 | <0.0001 |
| Control T2 vs. T3 | <0.0001 | <0.0001 |
| T1 intervention vs. control | 0.1852 | 0.7706 |
| T2 intervention vs. control | 0.9580 | 1.0 |
| T3 intervention vs. control | 0.7515 | 0.9996 |

Table II. *Maximum diameter and area of melanocytic naevi*

| Group | Timepoint | Diameter, mm Mean ± SD | Area, $mm^2$ Mean ± SD |
|---|---|---|---|
| Intervention | T1 | 1.68 ± 0.99 | 2.01 ± 4.50 |
| | T2 | 1.77 ± 0.81 | 2.03 ± 2.25 |
| | T3 | 1.98 ± 0.98 | 2.59 ± 3.67 |
| Control | T1 | 1.64 ± 0.97 | 1.89 ± 3.27 |
| | T2 | 1.88 ± 1.07 | 2.46 ± 4.32 |
| | T3 | 1.90 ± 1.03 | 2.48 ± 4.11 |

## DISCUSSION

Exposure to UV radiation can have harmful effects on the skin. Approximately 40–50% of lifetime UV exposure occurs before the age of 20 years (27). UV protection during childhood may play a significant role in primary prevention of skin cancer development in later life (12, 33).

The MN counts in childhood are influenced by sun exposure during family holidays (17, 20, 25). One study suggests that there might be a lag of approximately one year between holidays with high UV exposure and development of new MN (18). Children with a history of sunburn have significantly higher MN counts than those without sunburn (16, 33–35). The number of newly acquired MN during childhood can be considered a surrogate marker for UV exposure.

Several studies have been conducted to evaluate the number or density of MN, i.e. MN count per surface $m^2$, in children (Table SIII[1]). There is a complete lack of investigations in former East Germany; the present study is the first attempt. We observed a mean MN count of approximately 7 at age 3 years, with an increase to 20 3 years later. That is approximately 5 times the MN count reported in a large trial of 6–7-year-old children 5 years ago (17).

MN counts in children are strongly influenced by the attitude of their parents (25, 36, 37). Interventional studies for small children have therefore been focussing on the education of parents (38, 39). Interventions delivered to adult individuals or communities may increase sun-protection and cancer awareness (40, 41).

In the intervention group parents were informed about the hazards of uncontrolled UV exposure to their children and various measures of sun-protection. In contrast to our expectations, the educational efforts over 3 years did not result in reduced numbers of newly acquired MN in pre-school children. Similar results were observed in another trial (23).

Sun protection should focus on those anatomical regions with the highest increase in MN counts, i.e. face and ears, back and lower arms. The most effective protective measures resulting in lower MN counts are protective textiles and seeking shade (23–25).

There is much debate about the regular use of sunscreens, since this may result in lesser use of the other protective measures. In a randomized controlled trial from British Columbia, regular use of broad-spectrum sunscreen over 3 years resulted in a slight decrease in MN counts (median counts 24 vs. 28 – control; $p = 0.048$) (21). No protective effect on MN counts could be confirmed in other trials (23–25).

In contrast to other studies, neither gender, Fitzpatrick skin phototype nor hair and eye colour had a significant influence on the number of newly acquired MN. This might be due to geographical factors and genetic differences (42, 43). There is a tendency to higher MN counts in children with brown hair and brown eyes, Fitzpatrick skin type II to III, compared with those with a fairer skin complexion (44).

This is the first study in pre-school children using the tool of objective digital image analysis of pigmented lesions. Digital dermoscopy analysis offers several advantages, such as independence from the investigator, image storage, and comparability (30). The study demonstrates feasibility of mobile DB-MIPS analyser for screening purposes in children. The handling was easy and refusal of investigation by children was very uncommon.

The principle of this technology is a combination of computerized digital images obtained by epiluminescence dermoscopy and the mathematical analysis of multiple objective parameters by artificial neural network (46). In a previous study on differential diagnosis of pigmented lesions, DB-MIPS technology was superior to epiluminescence dermoscopy (47). With this advanced technology no atypical MN were observed.

The observation of disappearance of some MN at T2 and T3 can be interpreted through volatility of MN. The mechanisms involved are immune mechanisms (as in halo naevi), transepidermal elimination of melanocytes, or senescence driven by *BRAF* mutations (48).

In conclusion, significant increases in MN counts in pre-school children call for improved UV protection. The results of this study also support the argument that education can increase knowledge, but knowledge does not automatically change behaviour (49).

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