

Hair follicle punch grafts in hard-to-heal wounds: A monocenter study and patient survey

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Abstract

Background and Aims: Chronic wounds present a growing challenge in the aging population, resulting in an extended course of treatment and an increased influx of patients with recalcitrant wounds seeking admission to hospitals. Furthermore, the general trend in patient care is toward simple and inexpensive treatment methods, feasible in an outpatient setting with little material costs. This retrospective case study aims to elucidate the operative procedure and outcomes associated with hair follicle unit transplantation utilizing punch grafts from the scalp for the management of hard-to-heal wounds.

Methods: A cohort of 28 patients, comprising 20 males and eight females, with a mean age of 72.61 years (range: 48–89) and an average wound area of 82.49 cm², underwent dissection of punch grafts containing hair follicles (2–3 mm in diameter) from the scalp. Subsequently, these grafts were transplanted into the wound bed. The retrospective evaluation of ulcer healing encompassed photo documentation and clinical records, while patient satisfaction was assessed through structured questionnaires.

Results: In 78.6% (22) of the cases, a favorable impact on wound healing was observed, characterized by epithelization, and in 57.1% (16) of the patients, complete wound closure was achieved. With the exception of one donor site, all other sites healed without complications. The patient survey indicated that the majority of individuals subjected to the procedure did not perceive it as painful or time-consuming. Notably, 81% (17) of individuals expressed a willingness to undergo the treatment again. Even in challenging wound conditions, such as pyoderma gangrenosum, our method demonstrated a positive effect on wound healing.

Conclusion: Within our cohort, the utilization of hair follicle units in the management of hard-to-heal wounds resulted in either complete or partial wound closure for the majority of patients, accompanied by minimal morbidity, reduced operation time, and a low incidence of complications and associated costs.

Theresa M. Jansen, Sarah Janßen, and Norman-Philipp Hoff are contributed equally to this study. Theresa Jansen and Sarah Janßen share first authorship.

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KEYWORDS

chronic wounds, hair follicle punch grafts, hair follicle transplantation, hard-to-heal-wounds, wound healing

1 | INTRODUCTION

Chronic wounds pose a significant medical challenge, entailing substantial financial implications. Addressing these wounds necessitates interdisciplinary collaboration and effective patient management. In addition to conservative interventions like phase-appropriate wound care, surgical options, including split-thickness skin grafting, are considered for the treatment of recalcitrant ulcers. However, skin grafting often involves inpatient stays and extended hospitalization. An alternative surgical approach involves the transplantation of single skin punches with hair follicles, a highly efficacious procedure characterized by minimal trauma and suitability for outpatient settings.

Recent clinical and experimental studies have highlighted the positive impact of hair follicles and their perifollicular tissue on wound healing. This influence is attributed to factors such as the density of dermal stem cells, enhanced vascularization, and innervation. In patients with chronic wounds of the lower legs or surgical wound defects with donor sites on the occipital scalp, split-thickness skin grafts have demonstrated rapid wound healing.¹ Mouse models have further illustrated the accelerated wound closure and structural regeneration of the dermis associated with hair follicle stem cell transplantation, indicating increased expression of key factors such as SDF-1alpha, CXCR4, VEGFR-2, and keratinocyte growth factor.^{2,3}

Transplantation of hair follicle stem cells from the bulge region in mice leads to neovascularization, increased expression of growth factors like VEGF, TGF-beta, bFGF, and enhanced formation of collagen types 1 and 3.⁴ Transcriptome studies reveal differential responses of stem cells from the interfollicular epidermis (IFE) and the bulge region to wounds. Stem cells of the bulge region acquire a similar signature after trauma as those of the IFE migrate into the wound after 3–5 days, whereas IFE stem cells are already primed to respond to wound signals.⁵ Furthermore, hair follicle transplantation into scar tissue results in increased epidermal thickness, vessel density, and the inhibition of pro-fibrotic factors such as TGFβ1, IL-13, and IL-6, along with a reduction in inflammatory signals like IL-8, IL-6, and IL-1-alpha.^{6–8} The first commercially available hair-related therapy was EpiDex[®] (EuroDermBiotec & Aesthetics), an epidermis-equivalent sheet made by autologous outer root sheath keratinocytes from the patients, which has shown good results in chronic wounds.^{9,10}

Transplantation of single hair follicles in the setting of skin punching is a minimally invasive procedure with minimal costs. It has been studied in a limited number of clinical trials.^{11–14} Jimenez et al. demonstrated a reduction in ulcer area of nearly 30% after implantation of scalp hair follicle units at 18 weeks in 10 patient cases with chronic venous leg ulcers.¹³ In addition, the research group showed that wounds healed more quickly when hair follicle biopsies of the scalp were implanted compared to punch biopsies of hairless areas.^{12,15}

The present study aims to elucidate the procedural details and efficacy of a real-world treatment approach using punch grafts containing hair follicles to facilitate wound healing in diverse wound origins.

2 | MATERIAL AND METHODS

Between May 2020 and August 2022, a total of 28 patients with challenging-to-treat wounds from various etiologies underwent hair follicle unit transplantation at the Department of Dermatology at the University Hospital Duesseldorf. These wounds were associated with diverse underlying conditions, including pyoderma gangrenosum, necrobiosis lipoidica, and vasculitic ulcers. Notably, there is limited clinical data available in the existing literature pertaining to these specific wound types in conjunction with hair follicle unit transplantation, with only one study addressing two patients with pyoderma gangrenosum treated through this approach.¹⁴

We retrospectively assessed the transplantation outcomes using our clinical patient management system documentation (Medico[®]), photographic records, and distributed patient questionnaires.

The study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of the Heinrich Heine University Duesseldorf (Number 2022-2294).

2.1 | Surgical procedure

The transplantation is performed under sterile conditions in the operating room. Initially, the wound undergoes thorough cleansing, and the donor site at the posterior aspect of the head is appropriately shaved. Skin punches, with a diameter ranging from 2 to 3 mm and including adipose tissue, are harvested in the direction of hair growth from the donor site. Concurrently, skin punches are obtained from the wound bed area, serving as channels for the subsequent implantation of hair follicle units (Figure 1). The hair follicle unit biopsies are inserted into the punching channels with tweezers. Wound closure at the capillitium is performed with single button sutures. Following surgery, a gauze dressing (BSN medical Cuticell[®]) is applied on the recipient site. The first dressing change is performed on the 5th day postsurgery.

2.2 | Assessment for clinical outcomes

Clinical evaluations and photographic documentation were conducted at regular intervals during the dressing changes. Furthermore,



FIGURE 1 Figure 1 shows the surgical procedure. First, the punch biopsies are taken in the area of the hairy scalp (A), these are temporarily stored on a compress (B). The punch canals are taken in the area of the ulcer (C), after 1 week the engraftment is visible (D).

in December 2022, patients were provided with a questionnaire aimed at assessing subjective perceptions of wound healing, pain levels, and any limitations experienced in daily activities following the transplantation procedure.

3 | RESULTS

3.1 | Clinical outcomes

Table 1 presents the baseline clinical characteristics of the patient cohort. A total of 28 patients underwent hair follicle-containing punch graft transplantation, consisting of twenty males and eight females, with a mean age of 72.61 ± 10.73 years (median age 74; age range 48–89). The treated wounds exhibited considerable size, with a median area of 20 cm^2 and a mean area of $82.49 \pm 119.56 \text{ cm}^2$. Additionally, a prolonged duration of wound presence was observed, with a median duration of 11.5 months and a mean duration of 22.46 months (31.25 months).

The transplantation involved the implantation of 5–20 hair-containing units (median 8.5) with diameters ranging from 2 to 3 mm into the wound bed. Detailed information on the various wound types is presented in Table 2, encompassing venous ulcers (4; 14.29%), arterial ulcers (2; 7.14%), mixed ulcers (3; 10.71%), pyoderma gangraenosum (3; 10.71%), ulcerated necrobiosis lipoidica (2; 7.14%), vasculitic ulcers (2; 7.14%), Martorell ulcers (2; 7.14%),

TABLE 1 Patient characteristics.

Characteristics	n = 28
Age (years)	
Median (range)	74 (48–89)
Mean (SD)	72.61 (10.73)
Gender, n (%)	
Male	20 (71.43)
Female	8 (28.57)
Wound area (cm^2)	
Median (range)	20 (6.0–300)
Mean (SD)	82.49 (119.56)
Wound duration (months)	
Median (range)	11.5 (1–144)
Mean (SD)	22.46 (31.25)
Wound site, n (%)	
Lower leg	18 (64.26)
Foot	3 (10.71)
Scalp	7 (25)
SD, standard deviation	

Note: Sample demographic and clinical characteristics of the patients (n = 28).

TABLE 2 Wound types.

Characteristics	n = 28
Wound type, n (%)	
Venous ulcer	4 (14.29)
Arterial ulcer	2 (7.14)
Mixed ulcer	3 (10.71)
Pyoderma gangraenosum	3 (10.71)
Necrobiosis lipoidica	2 (7.14)
Vasculitis	2 (7.14)
Martorell ulcer	2 (7.14)
Scleroderma	1 (3.57)
Graft versus host disease	1 (3.57)
Postoperative wound healing disorder	8 (28.57)

Note: Different wound types of the patients (n = 28).

TABLE 3 Clinical outcome.

Outcome	n = 28
Wound healing, n (%)	
Positive effect	22 (78.6)
No benefit	6 (21.4)
Wound closure, n (%)	
Complete	16 (57.1)
Partial	6 (21.4)
None	6 (21.4)

Note: Clinical outcome in terms of wound healing and wound closure for all patients (n = 28).

Scleroderma (1; 3.57%), and Graft versus Host disease (1; 3.57%). Within our cohort, eight patients (28.57%) experienced postoperative wound healing disorders, primarily in hard-to-heal wounds located in challenging anatomical areas, particularly in the scalp region.

Table 3 delineates the clinical outcomes of the patients, categorized into the improvement of wound healing through the surgical procedure and complete closure. Among the 28 patients, 22 exhibited beneficial responses to the surgical intervention, while six wounds (of three male and three female patients) did not show improvement in wound healing. No explicit pattern indicating a diagnosis associated with a worse outcome was evident. Diagnoses related to a less favorable outcome included arterial occlusive disease, a mixed leg ulcer, a venous leg ulcer, Martorell's leg ulcer, scleroderma, and a scalp wound with radioderm. Notably, a prominent factor contributing to a less favorable outcome was identified as strong exudation, particularly evident in cases of venous and mixed leg ulcers.

The surgical procedure demonstrated efficacy across all patients with necrobiosis lipoidica, pyoderma gangrenosum, and vasculitis ulcers. Contrary to expectations, a large wound area did not emerge as a negative prognostic marker. The median size of wounds that benefited from grafting was 25 cm², whereas nonresponsive wounds had a median size of 11.63 cm². Additionally, the mean age of non-responders was 75.33 years, comparable to the overall average age of all transplanted patients (72.61 years).

3.2 | Clinical outcomes in different wound types

In our study, we addressed a diverse range of wounds, including chronic inflammatory wounds and vascular ulcers. It is essential to emphasize that, alongside grafting, we implemented targeted

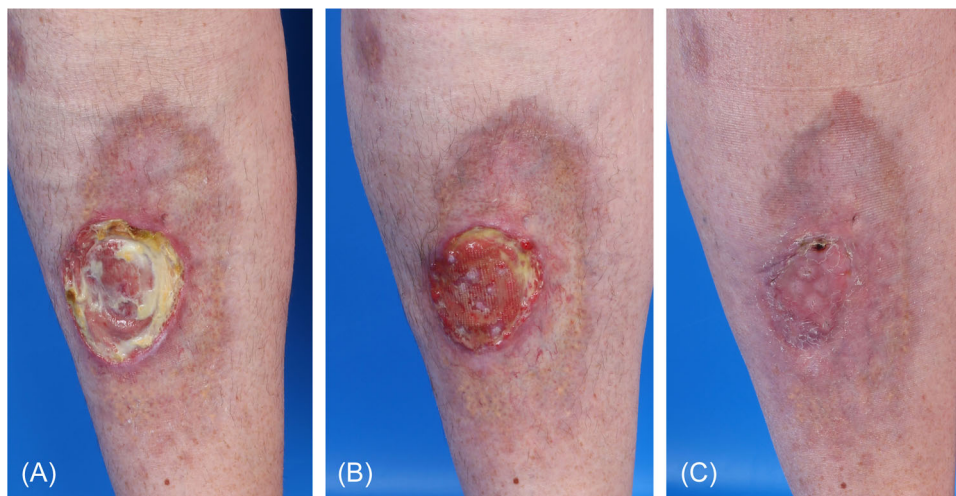


FIGURE 2 Clinical progression of a patient with an ulcerated necrobiosis lipoidica, depicting the condition before transplantation (A), after 2 months (B), and after 5 months (C). Notably, hair follicle grafting, involving 10 punches with a 2 mm diameter, resulted in an impressive reduction in the area and volume of the ulcerated necrobiosis lipoidica.

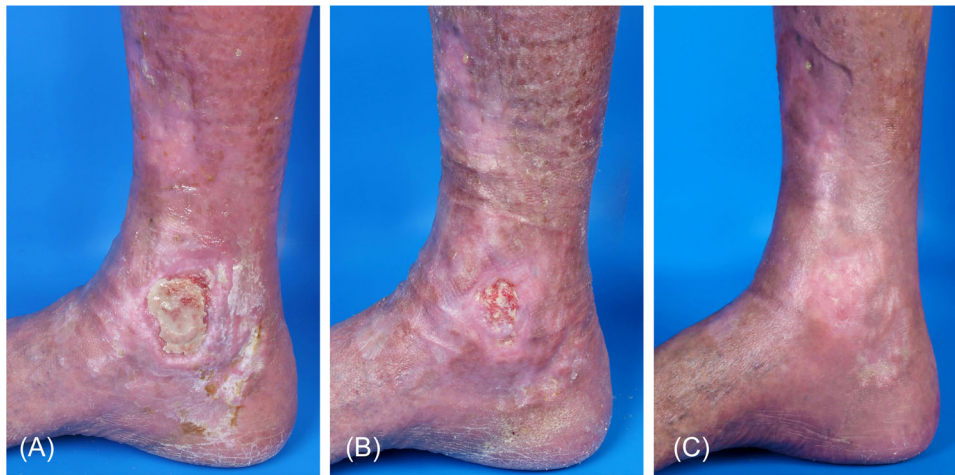


FIGURE 3 Patient with a chronic mixed ulcer before transplantation (A), after 10 months (B) and 14 months (C). Wound healing after transplanting 10 punches with a 3 mm diameter.

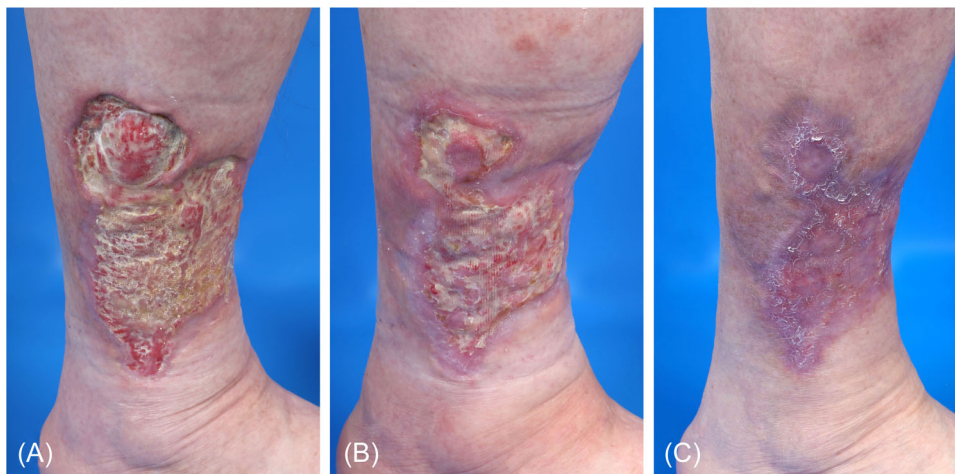


FIGURE 4 Patient with a pyoderma gangrenosum before transplantation (A), after 3 months (B) and 10 (C) months. Healing by transplantation of 6 hair follicle punch grafts with a diameter of 2 mm.

treatments addressing the underlying causes of the wounds. For instance, anti-inflammatory therapy was administered for atypical wounds, while compression therapy was employed for venous ulcers. This comprehensive approach proved effective in achieving favorable outcomes across wounds arising from vascular diseases and atypical conditions. We present the clinical course of wound healing for three patients in Figures (2–4).

3.3 | Complications

Overall, the procedure appears to be safe. Nevertheless, one patient required electrocautery due to postoperative bleeding at the back of the head (donor site). In light of this incident, we recommend suturing the wounds at the back of the head despite the small size of punch biopsies to mitigate the risk of bleeding. Apart from this specific case, no surgery-associated adverse events were observed. Three of our

patients died due to other diseases (Pancreatic cancer, esophageal variceal hemorrhage, and heart failure).

3.4 | Patient experience

According to the feedback obtained from patient experiences, a comprehensive questionnaire was administered, addressing various aspects of the transplantation procedure. The questionnaire encompassed evaluations of wound healing, complete healing, satisfaction with the extraction area (scalp), contentment with the new skin structure, pain levels, limitations in everyday life, and the renewed willingness to consent to the procedure.

Concerning wound healing, 49.9% of patients perceived significant improvement, while 23.8% noted slight improvement. Remarkably, 33.3% did not subjectively perceive any change, and no patient reported deterioration postsurgery. Eleven patients (52.4%) experienced

complete healing following transplantation. Regarding satisfaction with the donor site on the scalp, an overwhelming majority, comprising 95.2% of patients, reported high satisfaction, with only 4.8% expressing slight satisfaction. Concerning the skin structure, 42.9% of patients perceived an improvement, while an equal percentage did not, and 14.3% did not provide a response.

In terms of pain, 15 patients reported either no or minimal pain, while six classified their pain as moderate. No patient reported severe pain postsurgery. Postoperatively, 42.9% of respondents experienced mild limitations in their daily activities, and 57.1% reported no limitations. None of the respondents reported severe limitations in their daily lives. In conclusion, a significant majority (81%) expressed a willingness to undergo the transplantation procedure again. A detailed analysis of the questionnaire responses is presented in Table 4.

4 | DISCUSSION

Chronic wounds continue to be a substantial aspect of dermatological clinical care. In addition to established methods like autologous split-thickness skin grafting, various alternative surgical approaches are emerging to expedite wound closure. Notably, in Germany, the preference for outpatient interventions, even during the COVID-19 pandemic, highlights the need for minimally invasive, ambulant procedures with low trauma. Our study demonstrates the clinical efficacy of hair follicle-containing punch grafting as a rapid and patient-friendly option to stimulate wound healing, supported by high patient satisfaction, as evidenced by an 81% willingness to undergo the procedure again.

Compared to split-thickness skin grafting, this approach yields a robust skin structure and swift healing of the donor site, leading to high patient satisfaction (95.2%). Confocal microscopy illustrates a denser skin structure not only of the transplanted hair follicle organ but also in the surrounding area of about 1 cm around the graft (Figure 5).

The versatility of this minimally invasive surgical technique is highlighted by its successful application in atypical wounds, such as pyoderma gangrenosum, where surgical interventions are typically approached with caution. Importantly, patient age and wound area do not appear to be negative predictive factors. The six patients who did not benefit from the therapy had a comparable average age and rather smaller wounds than the other patients who responded. Patients who did not benefit from the therapy had a comparable average age and smaller wounds than responsive patients, suggesting that this therapy is applicable to older individuals. It has been shown that aging does not significantly alter the density of bulge hair follicle stem cells.¹⁶

In addition to the known benefit of hair follicles and their stem cells in accelerating wound healing, the impact on the wound microbiome remains an understudied but potentially crucial aspect. Transplantation of a complete follicular organ, inclusive of dense microbial material, may positively influence wound microbiome and enhance microbial resistance. This could also be a reason why

TABLE 4 Patient survey.

	n = 21
Wound healing, n (%)	
Strong worsening	0 (0)
Slight worsening	0 (0)
No change	7 (33.3)
Slight improvement	5 (23.8)
Strong improvement	9 (42.9)
Donor site, n (%)	
Very satisfied	20 (95.2)
Somewhat satisfied	1 (4.8)
Less satisfied	0
Not satisfied	0
Pain, (%)	
Non/hardly	15 (71.4)
Medium strong	6 (28.6)
Very strong	0 (0)
Limitations in daily life, n (%)	
strong	0 (0)
light	9 (42.9)
not at all	12 (57.1)
Complete healing, n (%)	
Yes	11 (52.4)
No	10 (47.6)
Better skin structure, n (%)	
Yes	9 (42.9)
No	9 (42.9)
No answer	3 (14.3)
Renewed concept, n (%)	
Yes	17 (81.0)
No	4 (19.0)

Note: Results of the patient survey (n = 21).

epithelialization does not only originate from the individual hair follicle islands, but also from the margin of the wound, what we see in the clinical courses. The change in the microfilm could be a positive stimulus for improved communication between the keratinocytes of the edge and the center. Further research is warranted in this area.

Our study underscores that the minimally invasive technique of hair follicle transplantation is effective and safe in chronic wounds caused by vascular diseases and atypical wounds resulting from chronic inflammatory processes. This therapy should be considered for elderly patients, given that aging does not significantly alter the density of bulge hair follicle stem cells.

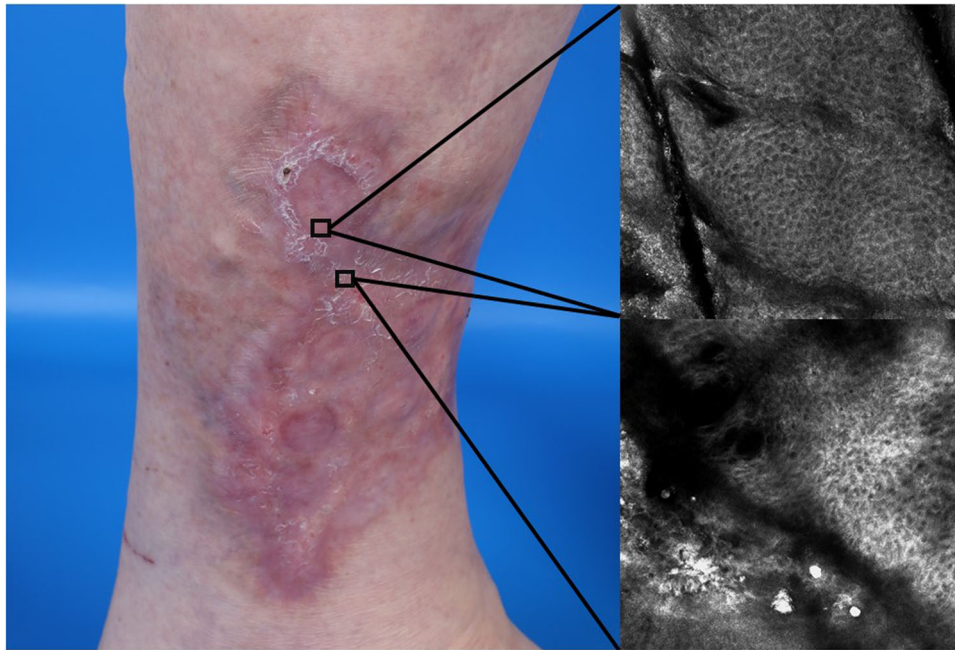


FIGURE 5 Clinical and confocal microscopy images of a patient with a pyoderma gangrenosum after complete wound closure due to transplantation of hair follicle units. The black squares denote the regions of interest for confocal microscopy, with the upper square indicating the newly formed skin that is directly adjacent to the transplanted hair follicle unit and the lower square representing second intention wound healing in the peripheral area resulting in scar tissue formation. In the upper right quadrant, the confocal microscopy image illustrates the structures of normal skin, specifically the transitional stage from the granular layer to the spinous layer. Conversely, the lower right quadrant depicts a thicker epidermis characteristic of scar tissue. In this region, there is a noticeable reduction in the density of epidermal cells, accompanied by altered cell morphology.

Despite current limitations and challenges, further research and larger clinical trials are needed to establish the therapy's clinical efficacy, safety, and contraindications. In conclusion, hair follicle-containing punch graft transplantation stands as a promising and transformative intervention for the management of chronic or hard-to-heal wounds of diverse origins, yielding improved patient outcomes and potential reductions in healthcare costs.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final version of the manuscript. Sarah Janßen had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available from corresponding author upon a reasonable request. The data are not publicly available due to privacy of ethical restriction.

TRANSPARENCY STATEMENT

The lead author Norman-Philipp Hoff affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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