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Serum Metabolites in Hand-Arm Vibration Exposed Workers

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Objective: To investigate whether low molecular organic biomarkers could be identified in blood samples from vibration exposed workers using a metabolomics. **Methods:** The study population consisted of 38 metalworkers. All participants underwent a standardized medical examination. Blood samples were collected before and after work shift and analyzed with gas chromatography time-of-flight mass spectrometry. Multivariate modeling (orthogonal partial least-squares analysis with discriminant analysis [OPLS-DA]) were used to verify differences in metabolic profiles. **Results:** Twenty-two study participants reported vascular symptoms judged as vibration-related. The metabolic profile from participants with vibration-induced white fingers (VWF) was distinctly separated from participants without VWF, both before and after vibration exposure. **Conclusion:** Metabolites that differed between the groups were identified both before and after exposure. Some of these metabolites might be indicators of health effects from exposure to vibrations. This is the first time that a metabolomic approach has been used in workers exposed to vibrations.

Keywords: Biomarkers, Hand-arm vibration, Metabolites, Vibration-induced white fingers

Learning Objectives

- Summarize the characteristics and diagnosis of the occupational disease known as vibration-induced white fingers (VWF).
- Outline the design and findings of the new evaluation of serum metabolites in workers exposed to hand-arm vibrations.
- Discuss the metabolomic study's possible implications for identifying potential biomarkers for harmful effects of hand-arm vibrations.

The use of handheld vibrating equipment may lead to an occupational disease called vibration-induced white fingers (VWF) or secondary Raynaud's phenomenon (SRP), and is the vascular part in hand-arm vibration syndrome (HAVS). Approximately 30% of work-related diseases causing a medical disability among the Swedish work force are suspected to be related to occupational exposure to hand-arm vibrations.[1]

Vibration-induced white fingers have been recognized for several decades, though it is still not fully understood whether hand transmitted vibrations initiate an injury to the nerves, the blood vessels, or an induced change in rheostatic properties of the blood in the exposed fingers.[2]

The diagnosis of VWF is determined following an interview about the occupational history regarding vibrations, symptoms regarding white fingers, and a clinical investigation. Further investigation can include a cold challenge test or measuring recovery time of skin temperature rewarming after cooling.[3,4] The severity of VWF is usually classified according to the Stockholm Workshop scale.[5,6]

When an individual suffering from this occupational disease is exposed to cold, there is a whiteness of the fingers often combined with severe pain. In addition, the disease may have a great impact on the individuals' social life, as many outdoor leisure time activities can no longer be carried out.

This increased susceptibility to vasoconstriction indicates that the blood vessels, the endothelium in the wall of the vessels, or the nerves in the fingers are affected following vibration exposure.[6] By the time the syndrome has manifested it is too late to perform technical measures at the workplace to minimize the workers' exposure to vibrations.[7]

It would thus be a great advantage to develop a clinical method which could be used, at an early stage, to evaluate whether a vibration-exposed worker is at risk of developing VWF.

Metabolomics is an approach by which dynamic changes in a series of endogenous small molecular related to metabolism of tissues, cells, or body fluids can be studied (hereafter referred to as metabolites). The purpose of metabolomics is to identify specific metabolites that can reveal insight into causes and mechanisms of diseases, identify early and sensitive biomarkers of disease and ultimately explore new diagnostic tools and methods.[8]

The aims of this study are to identify low molecular organic biomarkers in blood samples from vibration exposed workers using a metabolomic approach and to evaluate whether there is a difference in individual biomarkers between vibration-exposed workers with diagnosed VWF compared with vibration-exposed workers diagnosed as without VWF.

MATERIAL AND METHODS

Study Group

Thirty-eight (38) full-time shiftworkers from a Swedish forge participated in this study. The participation rate was 56% (38 of 68)

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Clinical Significance: Clinical Relevance: Metabolomics may provide methods for identification of potential biomarker for harmful effect of vibrations. Similar metabolic profiles were identified for workers with vibration-induced white fingers and workers with increased cold intolerance, suggesting related biological mechanisms. Increased cold sensitivity could thus be used as an early warning signal for VWF.

The study had financial support from Region Örebro County for the submitted work (OLL-554271).

The study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2016/044).

The authors have no competing interests in connection with this paper.

Contributorship statement: P.V., P.G., and K.E. conceived and designed the study. I.L.B. and A.H. did the main data analysis and J.H., P.V., K.E., and P.G. interpreted the results. All authors participated in the writing of the manuscript. All authors approved the final version.

Graff, Vihlborg, Hagenbjörk, Hadrévi, Bryngelsson, and Eriksson have no relationships/conditions/circumstances that present potential conflict of interest.

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in the units that were included in the study. The work tasks in these units were mainly grinding of the forged metal products.

Medical Examination

All participants answered a validated questionnaire concerning symptoms of hand-arm vibrations. The questionnaire is available in Swedish from the occupational medicine methodical collection (http://fhvmetodik.se/wp-content/uploads/2014/10/frageformular_hand_arm.pdf). The participants answered questions about hand symptoms to detect symptoms of white finger, neurological symptoms (tingling, numbness in hands), pain in the upper limbs, and other illness and medication. It also contains questions about whether the worker was exposed to vibration and for how many years.

The medical examination was carried out using a standardized procedure.[7] It contains an examination on the hands, used to diagnose Carpal tunnel syndrome and identify signs of vascular damage at the wrist, using Phalen, Tinells, and Allen tests. The examination attempted to diagnose vibration-related symptoms and find a differential diagnosis in the patient's symptoms.

The diagnosis of VWF was set by symptoms description and classified using the Stockholm Workshop scale. All of the participants were classified according to the Stockholm Workshop scale for vascular disorders and neurological disorders by using the questionnaire.[6,7] A participant was classified as having hand-arm vibration-related symptoms if he had neurological or vascular symptoms without any other non-vibration related disease that could explain the complaints (eg, cervical herniation, diabetic neuropathy, traumatic amputation).

Workers who described early onset of Raynaud's phenomena or had signs of rheumatic disease, for example, known diagnosis, swollen joint, or signs of connective tissue disease were classified as Non-VWF. Workers were also classified as VWF if they described increased cold sensitivity and classified as stage 0.5 of the Stockholm Workshop scale, if onset was after start of exposure and no other explanation could be found (eg, medication, nicotine use).

Exclusion criteria were complications of hypertension (either combined with other metabolic disease such as hypercholesteremic or diabetic or heart complication, ie, heart failure or ischemic heart disease). In addition, active treatment for rheumatic disease and diabetes were considered as exclusion criteria.

Exposure Assessment

The main task for the workers was grinding edges and unevenness of the forged items in addition to quality control of the finished products.

The vibration exposure was estimated by measuring the vibration level at a point close to where the operator placed his hand while working with the grinder, according to ISO 5349-1:2001.[9] The equipment used was a triaxial accelerometer (3023M2 Dylan Instruments, LA). The accelerometer was fastened on a mounting block and the block was attached to the grinder with hose clamps. Data from the triaxial accelerometer were collected using a handheld four-channel vibration analyzer (Svantek 106, Svantek, Warzawa, Poland). To calculate the vibration exposure during the day of blood sampling (acute exposure), an estimation of the duration of their use of tools in minutes during the workday was done by an occupational hygienist.

Blood Sampling

A syringe attached to a vacutainer was inserted into the antecubital vein in the right arm. A blood sample was collected in a plastic tube containing Ethylenediaminetetraacetic acid before and after the work shift. The sample was placed on a blood tube rocker for 30 seconds immediately after collecting and then centrifuged at 10 °C at 1500 × *g* for 15 minutes. Following centrifugation a serum sample was allocated in an Eppendorf tube by means of a calibrated pipette. The Eppendorf tube was kept in dry ice during the day (approximately −70 °C). At the end of the workday the samples were transferred into a −80 °C freezer until sent for analysis. During shipping to the laboratory, the samples were kept in a container with dry ice. When arriving to the lab the samples were immediately transferred to a −80 °C freezer where they were kept until analysis.

GC TOFMS/MS

Sample Preparation

The extraction procedure was done as previously described by.[10] In short, 900 μL of extraction buffer (90/10 v/v methanol:-water) including internal standards ([13C5]-proline, [2H4]-succinic acid, [13C5,15N]-glutamic acid, [1,2,3−13C3]-myristic acid, [2H7]-cholesterol, [13C4]-disodium R-ketoglutarate, [13C12]-sucrose, [13C4]-palmitic acid, [2H4]-butanediamine2HCl, and [2H6]-salicylic) were added to 100 μL of sample material. The sample was shaken for 3 minutes. Proteins were precipitated at +4 °C on ice. The sample was centrifuged at +4 °C (14,000 rpm) for 10 minutes. Two hundred microliter of supernatant was transferred to a micro-vial and the solvents were evaporated.

Derivatization: Thirty microliter μL of methoxyamine (15 μg/μL in pyridine) was added to the dried sample. The sample was shaken for 10 minutes. The derivatization reaction was initiated by keeping the sample at +70 °C for 1 hour. The reaction then proceeded for 16 hours at room temperature. Thirty microliter of N-methyl-N-(trimethylsilyl)trifluoracetamide (MSTFA) was added, the sample was shaken and left for 1 hour at room temperature. Thirty microliter of methyl stearate (15 ng/μL in heptane) was added before analysis.[10]

GC/TOFMS Analysis

One microliter of the reconstituted sample was analyzed using a 10 m × 0.18 mm fused silica capillary column with a chemically bonded 0.18 μm DB 5-MS UI stationary phase (J&W Scientific, Folsom, CA). The flow rate was 1 mL/min, the purge flow was turned on after 60 seconds with a flow of 20 mL/min. The sample was injected (injector temp 270 °C) in splitless mode onto an Agilent 6890 gas chromatograph equipped with a Pegasus III time-of-flight mass spectrometer (Leco Corp., St Joseph, MI) using a CTC Combi Pal autosampler (CTC Analytics AG, Switzerland).

The column temperature was held at 70 °C for 2 minutes, then increased by 40 °C min^{-1} to 320 °C, and kept there for 2 minutes. The column effluent was introduced into the ion source. The transfer line and the ion source temperatures were 250 and 200 °C, respectively. Ions were generated by a 70 eV electron. Since previous studies in mass spectrometry-based metabolomics have shown analytical drift,[11] this study was designed to minimize influence of analytical drift by designing a run order of samples where matched or dependent samples are kept together. The analysis was done at The Swedish Metabolomics Centre (SMC) (Umeå, Sweden).

Statistics

To present the background variables and symptoms among the participating individuals SPSS 22.0 (IBM, North Castle, NY) was used.

Multivariate Analysis

To evaluate the differences in metabolite content between different groups, multivariate modeling in SIMCA (version 14.1, Umetrics, Umeå, Sweden) was used.

To detect patterns, trends and possible outliers, initial inspections of the data set was first visualized using principal component analysis (PCA). Strong outliers were identified using Hotelling T^2 statistics. Moderate outliers were identified by the distance to the model plane (DModX).

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TABLE 1. Demographic Data of the 38 Participants in the Study

	VWF		Non-VWF		Total	
	N	%	*N*	%	*N*	%
Sex						
Male	22	100	16	100	38	100
Age groups						
<41	7	31.8	5	31.3	12	31.6
41–50	9	40.9	5	31.3	14	36.8
>51	6	27.3	6	37.5	12	31.6
Mean	44.8		45.1		44.6	
Median	45.5		46.0		45.0	
Min–max	26–58		28–62		26–62	
Employment years						
0–5	4	18.2	2	12.5	6	15.8
6–10	6	27.3	3	18.8	9	23.7
11–15	2	9.1	6	37.5	8	21.1
>15	10	45.5	9	31.3	15	39.5
Mean	12.7		13.9		13.2	
Median	12.0		14.0		13.5	
Min–max	1–33		1–37		1–37	
Smoking habits						
Non smoker	19	86.5	12	75	31	81.6
Smoker	2	9.0	3	18.8	5	13.2
Unknown	1	4.5	1	6.2	2	5.3
Snuff habits						
Non-snuff user	15	68.2	8	50.0	23	60.5
Snuff user	7	31.8	7	44.0	14	36.8
Unkown			1	6.0	1	2.6

The study group was divided into those with vibration-induced white finger (VWF) and those without VWF, according to their response in the questionnaire.

Processed GC-TOF-MS files from the analysis of metabolites were subjected to centering and unit variance scaling before analysis using orthogonal partial least-squares analysis with discriminant analysis (OPLS-DA), to statistically verify differences in metabolites between the two groups (VWF vs Non-VWF).[12] The default seven-fold cross-validation in the SIMCA software was used to determine the quality of the model. OPLS is a supervised multivariate regression and prediction method which separates the systemic variation in *X* (metabolites) into two parts, one part that is correlated (predictive) to *Y* (VWF vs Non-VWF) and one part that is uncorrelated (orthogonal) to *Y*. When working with discrete variables the method is called OPLS-DA and is useful for biomarker identification. In this process each variable in *X* is associated with a weight $w*$ for each model component, which represents the variable's covariation with *Y* in that component. In this study, $w*$ for the predictive component in combination with a *P*-value <0.05 (independent samples *t* test performed by SPSS 22.0) was considered significant. The *P*-values from the *t* test statistics were adjusted using the Benjamini Hochberg procedure for false discovery rate control.[13]

Ethical Considerations

The study protocol was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2016/044).

RESULTS

Demographic data of the study participants are shown in Table 1. One participant reported a suspected but not verified rheumatic disease that was not the result of vibration exposure. Two study participants had hypertension and two were excluded from further analysis: one because of diabetes/hypertension and one because of hypertension with heart disease (both also on angiotensin-converting enzyme [ace] inhibitor).

TABLE 2. Medical Symptoms Among the Individuals Participating in the Study, Classified According to the Stockholm Workshop Scale for Vascular Symptoms

Vascular Symptoms	Stadium According to Stockholm Workshop Scale	*N*	%
No attacks	0	16	39.5
Increased cold intolerance	0.5	13	36.8
Attacks affecting only the tips of the distal phalanges of one or more fingers	1	7	18.4
Occasional attacks of whiteness affecting the distal and middle phalanges of one or more fingers	2	2	5.3
Frequent attacks of whiteness affecting all of the phalanges of most of the fingers	3	0	0
As 3v and trophic changes	4	0	0
	Total	38	100

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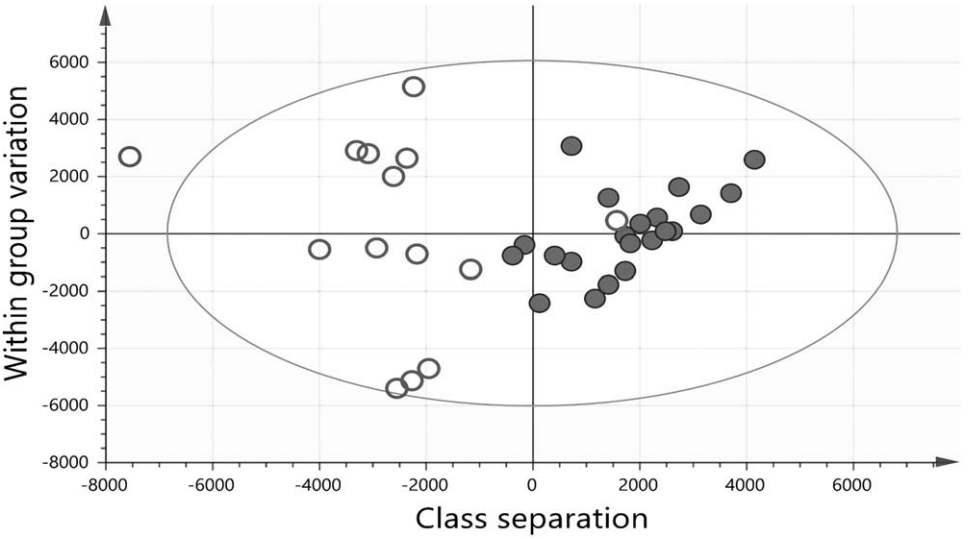

FIGURE 1. OPLS-DA score plot of serum metabolic profiling from workers with vibration-induced white fingers (filled circles) and workers without white fingers (open circles) before an acute vibration exposure (R2Y = 0.672, Q2 = 0.572, CV-ANOVA *P*-value = 0.000029). OPLS-DA, orthogonal partial least-squares analysis with discriminant analysis.

According to the medical examination, 16 persons were classified as Non-VWF and 22 were classified as VWF. Of the persons classified as VWF, seven were in stage 1, two in stage 2, and 13 persons were diagnosed with increased cold intolerance that had appeared after start of exposure (stage 0.5) (Table 2).

Vibration Exposure

The median exposure, calculated as daily exposure A(8),[9] for hand-arm vibration for all study participants was 1.6 m/s^2, with a maximum of 3.1 m/s^2. There were no statistically significant differences in hand-arm exposure during the day of measurement between the VWF and Non-VWF.

Metabolites Differentiating in Participants With VWF and Those Without VWF

To assess the difference in metabolic profile between individuals with VWF and those with Non-VWF, metabolites in serum were identified both before and after exposure to hand-arm vibrations. The gas chromatography time-of-flight mass spectrometry analysis resulted in 138 small molecules of which 72 metabolites were identified. A cross validated OPLS-DA model was used and two models with satisfactory predictive ability were identified. The samples from participants with VWF were distinctly separated from the samples from participants without VWF, in the comparison of the groups before the workday as well as after the workday (Figs. 1 and 2).

The OPLS-DA models revealed 10 identified metabolites that significantly (significant model weights [*w1*] and univariate significant *P*-value) differed between VWF participants and Non-VWF participants, before exposure to vibrations (Table 3).

The corresponding number of identified metabolites that were significantly different between participants with VWF and participants with Non-VWF after exposure to vibrations was 15 (Table 4).

Pathway Analysis

Pathway analysis was conducted on the metabolites found to be different between the VWF-group compared with those without VWF, according to the OPLS-DA analysis, both before and after vibration exposure. Metaboanalyst 4.0 was used for pathway analysis.[14] Several pathways were statistically significant according to

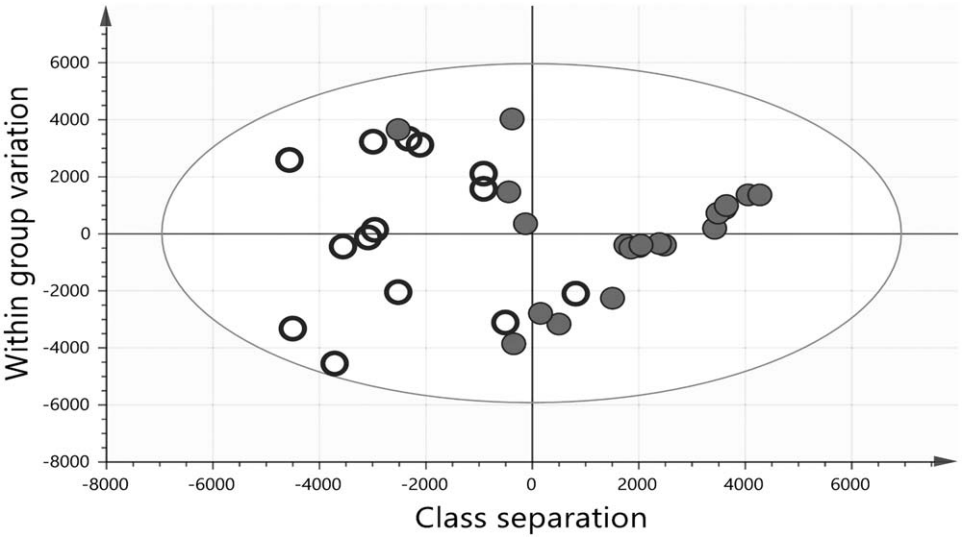

FIGURE 2. OPLS-DA score plot of serum metabolic profiling from workers with vibration induced white fingers (filled circles) and workers without white fingers (open circles) after an acute vibration exposure (R2Y = 0.587, Q2 = 0.417, CV-ANOVA *P*-value = 0.00278). OPLS-DA, orthogonal partial least-squares analysis with discriminant analysis.

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Fisher exact-test (see supplement files S1, http://links.lww.com/JOM/A726 and S2, http://links.lww.com/JOM/A727), however, when tested according to the Holm method only the Aminoacyl-t RNA biosynthesis, after exposure to hand-arm vibration, was statistically significant.[15] To exploit the study design with matched sample pairs (pre/post exposure) a novel multivariate statistical analysis method, orthogonal partial least squares effect projections (OPLS-EP),[11] was used, however this yielded no significant results.

DISCUSSION

To our knowledge this is the first time that GC-TOFSMS and OPLS-DA models have been used to investigate serum metabolites of workers exposed to hand-arm vibrations. In this study a different profile of low molecular organic metabolites in serum for workers with VWF versus workers without VWF, both before and after exposure to vibrations during work, was found.

Pathway analysis of the metabolites found in a significantly different abundance in serum from individuals with VWF compared with individuals without VWF are shown in Tables S1, http://links.lww.com/JOM/A726 and S2, http://links.lww.com/JOM/A727. The only statistically significant pathway after exposure to hand-arm vibration (Holm $P < 0.05$) was the Aminoacyl tRNA biosynthesis pathway, (Table S2, http://links.lww.com/JOM/A727). This pathway was also indicated to be of importance before hand-arm vibration exposure, however not statistically significant.

Several of the metabolites (Tables 3 and 4) and the Aminoacyl tRNA biosynthesis pathway (Table S2, http://links.lww.com/JOM/A727) are suggested to be of relevance in the biological mechanism for SRP: some of the metabolites identified are amino acids (argininne, glutamine, glycine, and lysine) which are involved in nitric oxide (NO) production, activation of leukocytes, and regulation of energy production. For changes in vascular response to stress (in this case due to vibrations) it has been suggested that leukocyte activation including endothelial damage, increased blood viscosity and vascular obstruction, reduced NO (less vasodilation) and oxidative stress (free radical formation with endothelial damage) are involved.[2,16,17]

NO is a known vasodilator for blood vessels, and an impaired vasodilation can cause a vasoconstriction of the vessels and thereby induce VWF.[2,17] Endothelia cells produce NO by endothelial nitric oxide synthase (eNOS), a process that involves arginine, an amino acid that was lowered in persons with VWF compared with Non-VWF after exposure. It is suggested that the mechanical impact from vibration or repeated reperfusion of the finger tissue produce reactive oxygen species (ROS) which can alter eNOS function, and that this dysfunction in NO regulation might cause vasospasm.[18] Previous studies shows that a decreased NO activity causes vascular dysfunction in digital arteries. A suspected mechanism could be an inhibition of nitric-oxide synthase due to the increased ROS level, but also sympathetic nerve system may affect the vasoconstriction.[19–21] Due to the shorter time to develop neurological symptoms compered to vascular symptoms it is possible that neurological impairment from vibration decrease neuronal nitric oxide synthase (nNOS) and onset vascular symptoms.[22] Further exposure for vibration and-/or cold ischemia from vascular constriction could give added sympthoms via eNOS and free radicals. It is also suggested that VWF patients who already have a tendency for vasospasm may develop an enhanced tissue ischemia because of activated leucocytes. This may lead to difficulties passing capillary structures.[17]

The aminoacyl-tRNA biosynthesis is thought to be of importance in autoimmune disease, such as Raynaud phenomenon. One theory is that vibration causes tissue damage that results in the release of autoantibodies which interact with aminoacyl tRNA.[23]

In the VWF individuals beta-D-glucopyranose and 4-deoxypyridoxine were significantly lowered compared with Non-VWF, both before and after exposure. 4-Deoxypyridoxine is an antagonist for pyridoxine (vitamin B6) and deficiency of B6 can produce symptoms of polyneuropathy, and effects immune response.[24,25] The presence of 4-deoxypyridoxine could thus be clinically relevant. Beta-D-Glucopyranose is lower in VWF individuals. This might be a result of an increased anaerobe metabolism due to the reduced blood flow in VWF.

The VWF-group that includes SRP and increased cold sensitivity had, as shown in Figures 1 and 2, a different metabolic profile. This suggests that physiological response differs in VWF-group compared with Non-VWF when exposed to vibration. It seems that all individuals within the VWF-group react in a similar manner, which may suggest that cold sensitivity can be a milder form of SRP. If so, cold sensitivity could be a first sign in developing VWF and workers should be advised to take precautions to minimize the vibration exposure.

The main strength of this study is that all participants were examined on the same day as the blood samples were collected on site. The main limitations of this study are that the number of

TABLE 3. OPLS-DA Significant Weights ([*w1*]) and Univariate Significant Metabolites Between VWF Versus Non-VWF Before Vibration Exposure

Metabolites	Loading Value	*P*-Value
beta-D-Glucopyranose	−0.863	0.023
4-Deoxypyridoxine	−0.080	0.017
N-FormylGlycine	−0.070	0.013
Glutamine [-H20]	−0.039	0.025
L-Threonic acid	−0.033	0.015
Aminomalonic acid	−0.032	0.011
Glyceric acid	−0.019	0.010
Lysine,N,N,O	0.018	0.042
Glycine,N,O	0.047	0.014
Cholesterol	0.062	0.016

Positive loadings values are metabolites more abundant in participants suffering from white fingers. Negative loadings values are metabolites more abundant in participants without white fingers. OPLS-DA, orthogonal partial least-squares analysis with discriminant analysis.

TABLE 4. OPLS-DA Significant Weights ([*w1*]) and Univariate Significant Metabolites Between VWF Versus Non-VWF After Vibration Exposure

Metabolites	Loadings Value	*P*-Value
beta-D-Glucopyranose	−0.852	<0.001
4-Deoxypyridoxine	−0.091	<0.001
N-FormylGlycine	−0.078	<0.001
Glutamine [-H20]	−0.045	0.007
L-Threonic acid	−0.038	0.008
Picolinic acid	−0.036	<0.001
Glycine	−0.035	0.030
Aminomalonic acid	−0.035	<0.001
Arginine	−0.023	0.046
Glyceric acid	−0.017	<0.001
Maltose	−0.017	0.031
Lysine	0.017	0.024
Pyroglutamic acid	0.022	0.027
Glycine	0.052	0.030
Cholesterol	0.081	<0.001

Positive loadings values are metabolites more abundant in participants suffering from white fingers and negative loadings values are metabolites more abundant in individuals without white fingers. OPLS-DA, orthogonal partial least-squares analysis with discriminant analysis.

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participants and the fact that metabolic profiles are known to be affected by a range of different factors,[26] but by using individuals without VWF as controls, some of the external factor such as time of day, outdoor temperature, and food intake could be limited.

CONCLUSION

The results presented in this paper suggest that workers with VWF have a different metabolic serum profile compared with vibration-exposed workers without VWF, both before and after work shift. The differences in the metabolic profile were found both in individuals who have SRP and in individuals who suffer from increased cold intolerance, which could suggest that the mechanisms of these symptoms could be related. Increased cold sensitivity is believed to be a prior stage to VWF and could thus be used as an early warning signal. Metabolomic may thus provide methods for identification of potential biomarker for harmful effect of vibrations.

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