Supplement to

Biological Variables Influencing the Estimation of Reference Limits

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Title and footnotes of table 2

Table 2 Influence of biological variables on the estimation of reference limits in individuals over 18 years of age. Abbreviations: n/a, not applicable; n.s., not significant; Spr, spring; Sum, summer; Fal, Fall; Win, winter.

Footnotes:

(1) Age or sex-specific effects are presumed if significant differences are stated in representative studies listed in reference column (a).

(2) Effects of posture are summarized as changes between supine position and either sitting or standing position or different degrees in head-up-tilt position. Effect of posture is presumed if significant changes in any of these positions have been stated in the respective studies listed in reference column (b).

(3) Populations have been stratified by gender and further divided in adults and elderly. Adults summarize males from 18 to 50 years of age and non-menopausal adult females, whereas elderly are defined as males older than 50 years and postmenopausal females. All categories only refer to columns that belong to diurnal and annual variations..

(4) The presence of a circadian rhythm for the respective population is shown as declared in the corresponding reference column (c).

(5) The time frame of peak and trough is derived from the reported fitted sinus or cosinus curves, respectively. Time was rounded to full clock hours. Trough and peak ± 3 hours encompass analyte concentrations below or above the 50 percent interquartile range, respectively, as estimated from the reported sinusoidal curve (for review see reference [220].

(6) Clinical relevance as stated by authors of references in column (a);

(*) Asterisks in column "clinical relevance" indicate that difference between peak and trough values (D_{xi}) exceeds permissible difference at the corresponding upper reference limit (pD_2) according to the concept of equivalence limits as described in the appendix and in reference [221]. Further details are shown in table 3.

(7) Seasonality is given as reported in the respective reference column (d). Calendar-based seasons for the northern hemisphere are shown.

(8) Additional information concerning clinical relevance given in references of column (c):

Albumin: fluctuations are interpreted as postural effect;

Total bilirubin: clinical relevance diurnal variation is assumed in ref. 24, however, p-value of the fitted cosine curve achieved borderline significant (p=0.052);

Total calcium: significant diurnal variation was given in 5 of 14 women and 3 of 13 men [49];

Adjusted total calcium, phosphate, osteocalcin: food intake is stated as major cause of diurnal variation [29,157];

Interleukin-6, TNF-α: risk of confounding in studies without time-qualified blood sampling;

Lymphocyte populations: variations are only discussed in terms of biological relevance [76,145];

Vitamin C, vitamin E, pro-vitamin A: pathophysiological relevance and impact on diet regimens have been hypothesized.

Title and footnotes of table 3

Table 3 Auxiliary data to assess clinical relevance of diurnality as described in the appendix. Clinical relevance is presumed if the difference between peak and trough (Dxi) exceeds permissible difference pD_2. Abbreviations: n/a, not applicable.

Footnotes:

(*) Asterisks mark absolute peak to trough values (Dxi) that exceed the permissible difference (pD_2) and thus indicates an impact of diurnal variation on given RL.

(°) Open circles mark analytes with clinical relevant diurnal variations as stated in supplemental table 2.

(1) MESOR, Midline Estimating Statistic Of Rhythm indicates the rhythm-adjusted mean of the respective analyte (see reference [220]).

(2) Peak-trough difference of best fitting cosine curves were extracted from the assigned reports in table 2 and either expressed as a percentage of the mesor in order to indicate and compare the extent of circadian variation and further as absolute concentrations (Dxi). See also explanations given in the appendix.

(3) pD_2, permissible difference at the corresponding upper reference limit, has been calculated as recently described [221]. Reference intervals needed for calculation of pD_2 are taken from references listed in column (a) or (c) of corresponding rows in table 2.

Title and legend of table 4

Table 4 Synopsis of search strategy. Measurand names and synonyms were initially aligned to entry terms provided by NML MeSH. NCBI MEDLINE database searches were performed between April to October 2017. Matches were manually reviewed according to the listed major and minor criteria. Mandatory criteria had to be met as precondition for review of major criteria. Major criteria have to be met to consider report for inclusion in this review. Minor criteria were used in addition for in depth quality assessment, in particular in case of several matches or conflicting results.

In case of >500 matches the common query term was modified as described (first line restriction). Modification of specific search terms (second line restriction) was necessary in some cases due to >500 matches even after first line restriction.

Appendix

The clinical relevance of diurnal variations is presumed in case that the difference between the maximum (peak) and minimum (trough) value is larger than the equivalence limit as described in ref. [222]. In some cases, it has been assumed that troughs are located ± 12 hours before and or after peak values of reported acrophases if 24 hours periodicity of the analyte is known. In other cases, peaks and troughs of table 2 were estimated from figures of the respective reports, if no other information were available.

For example, with troponin T the peak value of 16.2 ng/L occurred at 8:30 am and the minimum of 12.1 ng/L at 7:30 pm in a cohort of 24 individuals without a recent history of acute myocardial infarction [223]. The difference (D) of 4.1 exceeds the range of equivalence limits (pD_2) of 1.912 for the given RL (see below).

Equivalence limits have been proposed [220] to evaluate the relevance of the difference between two reference intervals. The permissible difference (pD_{xi}) [220] is defined as:

$$pD_{XI} \leq + ps_{A,XI} \cdot 1.28 \quad (1)$$

The permissible analytical standard deviation (psA) for a measured value (x_i) , i.e. (ps_{AXI}), was derived as recently described [222].

In the case of troponin T,

a reference interval of 5.0 to 13.8 ng/L has been presumed [204], (2)

a trough value of 12.1 ng/L and (3)

a peak value of 16.2 ng/L was reported (D = 4.1) [223], (4)

psA,xi = 0.7468 (x_i = 16.2) and (5)

the permissible difference at the upper RL (pD_2) becomes 17.4 – 14.9 = 2.5. (6)

Because D > pD_2, clinical relevance is assumed. (7)

Note to equation (5): ps_{AXI} results from a Microsoft Excel spreadsheet calculation form [222,224] that is online available at the homepage of the German Society of Clinical Chemistry and Laboratory Medicine (https://www.dgkl.de).

Supplemental Table 2

Analyte	Gender[(a)(1)]	Age[(a)((1)]	Posture (b) as compared to supine position[(2)]	Diurnal variations (c) Population[(3)] [Age, Gender]	Diurnal Rhythm[(4)]	Clock hours[(5)] Peak	Clock hours[(5)] Trough	Clinical Relevance[(6)]	Annual seasonal variations[(7)] (d) Min	Annual seasonal variations[(7)] (d) Max	References (a)	References (b)	References (c)	References (d)
17-β-estradiol	yes	yes	no data	elderly, female	yes	10 to 16	22 to 04	yes	n.s.		1	-/-	2	2, 3
17-hydroxy- progesterone	yes	yes	no data	elderly, male	yes	03 to 09	15 to 21	yes*	n.s.		4	-/-	2	2
				elderly, female	yes	02 to 08	14 to 20	yes*					2	
α-1-antitrypsin	none	none	increase	adults, mixed	yes	07 to 13	19 to 01	yes	Sum	Win	5	6	7	7
α-2-macroglobulin	yes	yes	increase	adults, mixed	no	n/a	n/a	n/a	no data		8	6	7	-/-
ACTH	yes	yes	increase	elderly, male	yes	05 to 11	17 to 23	yes*	Fal	Sum	1,9,10	11	2	12
	no			elderly, female	yes	02 to 08	14 to 20	yes*			10		2	
aPTT	yes	yes	none	adults, mixed	yes	19 to 01	07 to 13	yes	n.s.		13	14	7	15
				adults, mixed	no	n/a	n/a	n/a					16	
ALAT	yes	yes	increase	adults, male	no	n/a	n/a	n/a	Spr-Sum	Win	17,18	19	20	21
		none		adults, mixed	yes	18 to 24	06 to 12	not stated			22		23	
				adults, male	no	n/a	n/a	n/a					24	
Albumin	yes	yes	increase	adults, mixed	yes	13 to 19	01 to 07	yes	Win	Sum	1,25	19,26	27	28
	none			elderly, female	yes	13 to 19	01 to 07	none[(8)]*			22		29	
				adults, male	no	n/a	n/a	n/a					24	
Aldosterone	none	yes	increase	elderly, male	yes	04 to 10	16 to 22	yes*	Sum	Win	1	30	2	31
				elderly, female	yes	03 to 09	15 to 21	yes*					2	
				adults, mixed	yes	03 to 09	15 to 21	yes*					32	
Alkaline phosphatase (AP)	yes	yes	increase	adults, mixed	yes	17 to 23	05 to 11	not stated	n.s.		1	19,26	23	21
	none	none		adults, male	no	n/a	n/a	n/a			22		24	
Amylase, pancreatic	yes	yes	increase	adults, male	no	n/a	n/a	n/a	n.s.		33,34	19,26	20	35
	none	none		adults, mixed	no	n/a	n/a	not stated			22		23	
ANP $_{(99-126)}$	yes	yes	Increase/ decrease	adults, male	yes	04 to 10	16 to 22	yes*	no data		36	37 38	24	-/-

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Annual seasonal variations[7] (d) Max	References (a)	References (b)	References (c)	References (d)
pro-ANP (1-30)	yes	yes	decrease	adults, male	yes	03 to 09	15 to 21	yes*	no data		39,40	41	24,42	-/-
31 - 67 pro-ANP (31-67)	no data		no data	adults, male	yes	03 to 09	15 to 21	yes*	no data		-/-	-/-	24,42	-/-
Antithrombin	yes	yes	no data	adults, mixed	no	n/a	n/a	n/a*	n.s.		43	-/-	7	44,45
				elderly, male	yes	10 to 16	22 to 04	yes*					46	
				adults, male	yes	12 to 18	24 to 06	yes					46	
ASAT	yes	none	increase	adults, mixed	yes	15 to 21	03 to 09	not stated	Fal	Spr	17,34	19	23	21
				adults, male	yes	13 to 17	01 to 05	none			47		20	
				adults, male	no	n/a	n/a	n/a					24	
Bilirubin, total	none	none	increase	adults, male	yes	06 to 12	18 to 24	none	n.s.		47	19	20	48
				adults, male	no	n/a	n/a	yes[8] *					24	
Bone-specific- AP (BAP)	yes	yes	no data	elderly, female	yes	09 to 15	21 to 03	yes	Sum	Win	49,50	-/-	51	52
				elderly, male	yes	10 to 16	22 to 04	yes	Sum	Win			51	52
C-peptide	none	yes	no data	elderly, male	yes	13 to 19	01 to 07	yes*	Win-Spr	Sum-Fal	53,54	-/-	2,53	2
				elderly, female	yes	13 to 19	01 to 07	yes*					2	
				adults, male	yes	15 to 21	03 to 09	yes*					55	
CRP, high-sensitive	yes	yes	none	adults, mixed	no	n/a	n/a	n/a	Sum-Fal	Win-Spr	22,56	19	57	58
				adults, mixed	yes	12 to 18	24 to 06	yes*	Sum	Win			59	59
Calcium, total	none	none	increase	elderly, female	yes[8]	10 to 16	22 to 04	not stated[8]	Sum	Win	22,33	19,26	51	60
	none	none		elderly, male	yes[8]	11 to 17	23 to 05	not stated[8]					51	
	none	none		adults, mixed	yes	02 to 08	14 to 20	yes*					61	
	none	none		adults, male	no	n/a	n/a	n/a					24	
Calcium, adjusted total	none	yes	no data	elderly, female	yes	07 to 13	05 to 11	none[8]	no data		33	-/-	29	-/-
Calcium, ionized	yes	none	none	adults, mixed	no	n/a	n/a	n/a	Win	Sum	62	63	24	64,65
	none										22			
Chloride	none	none	none	adults, male	no	n/a	n/a	n/a	n.s.		47	19	24	60
Cholinesterase, Pseudo-	yes	yes	no data	adults, mixed	yes	13 to 19	01 to 07	not stated	n.s.		66	-/-	23	67
Cholesterol, total	yes	yes	increase	adults, mixed	yes	13 to 19	01 to 07	not stated*	Sum	Win	22,68,69	19,26, 70,71	72	73

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position(2)	Diurnal variations (c) Population (3) [Age, Gender]	Diurnal Rhythm(4)	Clock hours(5) Peak	Clock hours(5) Trough	Clinical Relevance(6)	Annual seasonal variations(7) (d) Min	Annual seasonal variations(7) (d) Max	References (a)	References (b)	References (c)	References (d)
				adults, mixed	yes	15 to 21	03 to 09	not stated*					72	
				adults, mixed	yes	13 to 19	01 to 07	not stated*					72	
				elderly, mixed	yes	12 to 18	24 to 06	not stated*					72	
				adults, male	yes	10 to 16	22 to 04	yes					55	
				adults, male	no	n/a	n/a	n/a					24	
				adults, male	no	n/a	n/a	n/a					24	
Cortisol	yes	yes	increase	elderly, male	yes	05 to 11	17 to 23	yes	Spr	Win	4	11,74	2	75,12
				elderly, female	yes	03 to 09	15 to 21	yes*	n.s.				2	12
				adults, male	yes	07 to 13	19 to 01	yes*					76	
				adults, mixed	yes	04 to 10	16 to 22	yes*					32	
				adults, male	yes	04 to 10	16 to 22	yes*					24	
Creatine kinase	yes	yes	increase	adults, mixed	yes	15 to 21	03 to 09	not stated	Fal	Spr	22,77,78	19,26	23	79
				adults, mixed	yes	11 to 17	23 to 05	not stated					23	
				adults, male	yes	12 to 18	24 to 06	none*					20	
Creatinine	yes	yes	none	elderly, female	yes	11 to 17	09 to 15	not stated*	Win	Sum	1,22,33	19	29	21
				adults, male	yes	19 to 01	07 to 13	yes*					24	
				adults, male	no	n/a	n/a	n/a					20	
Cystatin C	yes	yes	increase	adults, male	yes	03 to 07	09 to 14	none	no data		80	81	82	-/-
D-Dimer	none	yes	none	adults, mixed	no	n/a	n/a	n/a	Sum	Win	83	84	59	59
	yes										59			
DHEAS	yes	yes	no data	elderly, male	yes	09 to 15	21 to 03	yes	Spr-Sum	Win	4	-/-	2	
				elderly, female	yes	08 to 14	20 to 02	yes	Spr-Sum	Win			2	2
Dopamine	no data	yes	none	mixed, male	yes	01 to 07	13 to 19	yes*	Fal-Spr	Sum	85,86	87	88,89	12
				mixed, female	yes	01 to 07	13 to 19	yes*					88	
Epinephrine	yes	none	increase	adults, mixed	yes	16 to 22	04 to 10	yes*	Sum	Win	90,91	87,92	85,93	94
				adults, male	yes	13 to 19	01 to 07	yes*					76	
Erythrocytes	yes	yes	increase	adults, male	yes	02 to 08	14 to 20	yes	n.s.		95	96	24	48
				adults, male	yes	09 to 15	21 to 03	yes	Win	Sum			97	98

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Max	References (a)	(b)	(c)	(d)
MCH	none	yes	none	adults, male	no	n/a	n/a	n/a	Fal	Spr	95	96	24	99
				adults, male	no	n/a	n/a	n/a	Sum	Win			97	98
MCV	none	yes	none	adults, male	yes	21 to 03	09 to 15	yes	Fal	Spr	95	96	24	99
				adults, male	no	n/a	n/a	n/a	Sum	Win			97	98
MCHC	yes	none	none	adults, male	yes	11 to 17	23 to 05	yes	Fal	Spr	95	96	24	99
				adults, male	no	n/a	n/a	n/a					97	
RDW-CV%	none	yes	no data	adults, male	no	n/a	n/a	n/a	Win	Sum	95	-/-	24	99
				adults, male	no	n/a	n/a	n/a					97	
Factor II, activity	yes	none	no data	adults, mixed	no	n/a	n/a	n/a	no	data	100,101	-/-	16	-/-
Factor V, activity	none	yes	no data	adults, mixed	no	n/a	n/a	n/a	no	data	100, 101	-/-	7, 16	-/-
Factor VII, activity	yes	yes	no data	adults, mixed	no	n/a	n/a	n/a	Win	Sum	100, 101	-/-	102,16	103
Factor VII, antigen			no data	adults , male	yes	17 to 23	08 to 14	not stated	n.s.			-/-	102	104
Factor VIII:C, activity	none	yes	no data	adults, male	yes	05 to 11	17 to 23	yes	no.data		100	-/-	7	-/-
	yes			adults, male	no	n/a	n/a	n/a			101		16	
Factor VIII:CAg, antigen				adults, mixed	no	10 to 16	22 to 04	n/a*					105	
Factor IX, activity	yes	yes	no data	adults, mixed	no	n/a	n/a	n/a	no data		100	-/-	16	-/-
Factor X, activity	yes	none	no data	adults, mixed	no	n/a	n/a	n/a	no data		100	-/-	16	-/-
Factor XI, activity	yes	yes	no data	adults, mixed	no	n/a	n/a	n/a	no data		100	-/-	16	-/-
Factor XII, activity	yes	none	no data	adults, mixed	no	n/a	n/a	n/a	no data		100	-/-	16	-/-
Ferritin	yes	yes	no data	adults, male	no	n/a	n/a	n/a	Spr-Sum	Fal-Win	22, 106,107	-/-	97	108
Fibrinogen (Clauss)	none	yes	increase	adults, mixed	yes	05 to 11	17 to 23	yes	Sum	Win	22,109	110	7	59
				adults, mixed	no	n/a	n/a	n/a					16	
Folate	none	yes	no data	adults, male	yes	10 to 16	22 to 04	yes*	n.s.		111, 22	-/-	97	112
FSH	yes	yes	no data	elderly, male	yes	07 to 13	19 to 01	yes	Win	Sum	100,113	-/-	2	2
				elderly, female	no	n/a	n/a	n/a	Sum	Win			2	2
				adult, male					Fal	Spr				114
				adult, female					cycle	depend.				115

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position(2)	Diurnal variations (c) Population (3) [Age, Gender]	Diurnal Rhythm(4)	Clock hours(5) Peak	Clock hours(5) Trough	Clinical Relevance(6)	Annual seasonal variations(7) (d) Min	Annual seasonal variations(7) (d) Max	References (a)	References (b)	References (c)	References (d)
γ-GT	yes	yes	increase	adults, mixed	yes	15 to 21	03 to 09	not stated	n.s.		20, 22,34	19	23	48
				adults, male	no	n/a	n/a	n/a*					24	
				adults, male	no	n/a	n/a	n/a					20	
Gastrin	yes	yes	none	adults, male	yes	16 to 22	04 to 10	yes*	n.s.		116	117	24,118	119
Glucose, non-fasting	yes	yes	none	adults, male	yes	15 to 21	03 to 09	yes*	Spr	Fal	54	19	24	21
	none			adults, male	yes	21 to 03	09 to 15	yes*			22		55	
HBA1c	yes	yes	no data	adults, male	no	n/a	n/a	n/a	Sum	Win	120	-/-	55	121,122
HDL-C	yes	yes	increase	adults, male	no	n/a	n/a	n/a	Sum	Win	68, 69	70,71	55	73
		none		adults, mixed	yes	13 to 19	01 to 07	not stated*			22		72	
				adults, mixed	yes	14 to 20	02 to 08	not stated*					72	
				adults, mixed	yes	13 to 19	01 to 07	not stated*					72	
				elderly, mixed	yes	12 to 18	24 to 06	not stated*					72	
				adults, male	no	n/a	n/a	n/a					24	
Hematocrit	yes	yes	increase	adults, male	no	n/a	n/a	n/a	n.s.		95	19	24	58,98
				adults, male	yes	09 to 15	21 to 03	yes					97	
Hemoglobin	yes	yes	increase	adults, male	no	n/a	n/a	n/a	n.s.		22,95	19	24	58
				adults, male	yes	09 to 15	21 to 03	yes*	Spr	Fal			97	98
Human growth hormone	none	none	increase	elderly, male	yes	20 to 02	08 to 14	yes*	Win	Spr	123,124	125	2	126
	yes			elderly, female	no	n/a	n/a	n/a*			91		2	
Immunoglobulin G	none	none	increase	elderly, mixed	yes	11 to 17	23 to 05	yes*	no data		127	128	46	-/-
		yes									22			
Immunoglobulin A	none	none	increase	elderly, mixed	yes	10 to 16	22 to 04	yes*	no data		127	128	46	-/-
		yes									22			
Immunoglobulin M	yes	none	increase	elderly, mixed	yes	10 to 16	22 to 04	yes	no data		127	128	46	-/-
		yes									22			
Insulin	none	yes	no data	elderly, male	yes	13 to 19	01 to 07	yes*	n.s.		53, 54	-/-	2	129
				elderly, female	yes	13 to 19	01 to 07	yes*					2	
				adults, male	yes	14 to 20	02 to 08	yes*					24	

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Annual seasonal variations[7] (d) Max	References (a)	References (b)	References (c)	References (d)
Interleukin-6	none	yes	no data	mixed, mixed	yes	17 to 02	09 to 10	yes[8]*	Spr	Win	130,131	-/-	132	12
									Sum	Win				133
Iron	yes	yes	increase	adults, male	yes	07 to 13	19 to 01	yes*	Win-Spr	Sum-Fal	22,134	19	97	108
LDH	none	yes	increase	adults, male	yes	13 to 19	01 to 07	none*	Win	Sum	135	19	20	21
		none		adults, male	no	n/a	n/a	n/a			22		24	
				adults, mixed	yes	15 to 21	03 to 09	not stated					23	
LDL-C	yes	yes	increase	adults, male	yes	6 to 12	18 to 24	yes	Sum	Win	68,69	70,71	55	73
				adults, male	no	n/a	n/a	n/a					24	
Leptin	yes	yes	no data	elderly, male	yes	21 to 03	09 to 15	yes*	n.s.		136,137	-/-	138	139
Leukocytes	none	none	none	adults, male	yes	19 to 01	07 to 13	yes*	Sum	Fal	95	96	97	140
				adults, male	no	n/a	n/a	n/a*	n.s.				24	141
Basophils, rel.	none	none	none	adults, male	no	n/a	n/a	n/a*	Sum	Win	95	96,142	24	98
Basophils, abs.	none	none		adults, male	no	n/a	n/a	n/a					97	
				adults, male	yes	20 to 02	08 to 14	yes*					24	
Eosinophils, rel.	yes	none	none	adults, male	no	n/a	n/a	n/a	Win	Sum	95	96, 142	24	98
Eosinophils, abs.	yes	none		adults, male	yes	23 to 05	11 to 17	yes*					24	
				adults, male	yes	22 to 04	10 to 16	yes*					97	
Neutrophils, rel.	none	none	none	adults, male	yes	12 to 18	24 to 06	yes*	Fal	Spr	95	96, 142	24	98
Neutrophils, abs.	none	none		adults, male	yes	14 to 20	02 to 08	yes*					24	
				adults, male	yes	16 to 22	04 to 10	yes*					97	
Monocytes, rel.	yes	yes	none	adults, male	yes	06 to 12	18 to 24	yes	Fal	Spr	95	96, 142	24	98
Monocytes, abs.	yes	none		adults, male	no	n/a	n/a	n/a					24	
				adults, male	yes	20 to 02	08 to 14	yes*					97	
Lymphocytes, rel.	none	none	none	adults, male	yes	23 to 05	11 to 17	yes*	Spr	Fal	95	96, 142	24	98
Lymphocytes, abs.	none	yes		adults, male	yes	22 to 04	10 to 16	yes*					24	
				adults, male	yes	21 to 03	09 to 15	yes*					97	
Lymphozyte subpopulations														
T-Lymphocytes (CD3+)	yes	yes	no data	adults, male	yes	23 to 05	11 to 17	not stated[8]*	Sum-Fal	Spr	143	-/-	76	144

Analyte	Gender[(a)(1)]	Age[(a)((1)]	Posture (b) as compared to supine position[(2)]	Diurnal variations (c) Population [(3)] [Age, Gender]	Diurnal Rhythm[(4)]	Clock hours[(5)] Peak	Clock hours[(5)] Trough	Clinical Relevance[(6)]	Annual seasonal variations[(7)] (d) Min	Annual seasonal variations[(7)] (d) Max	References (a)	References (b)	References (c)	References (d)
CD4+ T-helper ceIIs	yes	none			yes	23 to 05	11 to 17	not stated[(8)]*	Sum	Win	143		76	144
-Naive CD4+ T-helper ceIIs	none	yes			yes	23 to 05	11 to 17	not stated[(8)]*			143		76	
-Central memory CD4+ T-helper ceIIs	none	yes			yes	23 to 05	11 to 17	not stated[(8)]*			143		76	
-Effector memory CD4+ T-helper ceIIs	yes	yes			yes	22 to 04	10 to 16	not stated[(8)]*			143		76	
-Terminal Effector CD4+ T-helper ceIIs	none	yes			no	n/a	n/a	n/a			143		76	
-CD8+ cytotoxic T cells	none	yes		adults, male	yes	23 to 05	11 to 17	not stated[(8)]*	Sum	Win	143		76	144
-Naive CD8+ cytotoxic T cells	none	yes			yes	23 to 05	11 to 17	not stated[(8)]*			143		76	
-Central memory CD8+ cytotoxic T cells	none	yes			yes	23 to 05	11 to 17	not stated[(8)]*			143		76	
-Effector memory CD8+ cytotoxic T cells	none	yes			yes	22 to 04	10 to 16	not stated[(8)]*			143		76	
-Terminal Effector CD8+ cytotoxic T cells	none	yes			yes	12 to 18	24 to 06	not stated[(8)]			143		76	
B-Lymphocytes (CD19+)	yes	none	no data	adults, male	yes	23 to 05	11 to 17	not stated[(8)]*	Sum	Win	143	-/-	145	146
Natural-killer cells	yes	none	no data	adults, male	yes	15 to 21	03 to 09	not stated[(8)]*	Spr	Fal	143	-/-	145	144
LH	yes	yes	no data	elderly, male	no	n/a	n/a	n/a	Fal	Win	1,113	-/-	2	2
				elderly, female	no	n/a	n/a	n/a	Fal	Spr			2	2
				adult, male					n.s.					114
				adult, female					cycle depend.					115
Lipase	none	none	no data	adults, mixed	no	n/a	n/a	n/a	no data		147	-/-	23	-/-
		yes									22			
Lipoprotein (a)	none	none	increase	elderly, male	yes	06 to 12	18 to 24	yes	no data		69	70	148	
Magnesium	yes	yes	increase	adults, male	no	n/a	n/a	n/a	Win	Spr	149	19	20	60
	none	none		adults, male	no	n/a	n/a	n/a			22		24	
Melatonin	none	yes	increase	adults, male	yes	00 to 06	12 to 18	yes*	Spr-Fal	Win	150,151	126	24	152

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Annual seasonal variations[7] (d) Max	References (a)	References (b)	References (c)	References (d)
				adults, male	yes	00 to 06	12 to 18	yes*					55	
Myoglobin	yes	yes	no data	adults, male	yes	06 to 09	18 to 24	yes*	no data		153,154	-/-	153	-/-
				adulds, female	yes	06 to 09	18 to 24	yes*					153	
Norepinephrine	yes	none	increase	adults, male	yes	11 to 17	23 to 05	yes*	Sum	Win	90,91	92, 87	76, 85	94
Osteocalcin	yes	yes	none	elderly, female	yes	21 to 03	09 to 15	yes	Sum	Win	101,155	156	51	52
				elderly, male	yes	22 to 04	10 to 16	yes	Sum	Win			51	52
				adults, female	yes	01 to 07	13 to 19	none[8]	n.s.				157	158
Osteoprotegerin	yes	yes	no data	elderly, male	yes	09 to 15	21 to 03	yes*	n.s.		101,159	-/-	160	161
				adults, female	yes	09 to 15	21 to 03	yes*					160	
				elderly, female	yes	12 to 18	24 to 06	yes*					160	
				adults, female	no	12 to 18	24 to 06	n/a					157	
iPTH, 1-84	none	yes	increase	elderly, female	yes	21 to 03	09 to 15	yes*	Sum	Win	162	163	51	52,65
				elderly, male	yes	18 to 24	06 to 12	yes*	Sum	Win			51	52,65
				elderly, male	yes	21 to 03	09 to 15	yes*					160	
				adults, female	yes	00 to 06	12 to 18	yes*					160	
				elderly, female	yes	21 to 03	09 to 15	yes*					160	
				elderly, female	yes	17 to 23	07 to 13	yes*					29	
Phosphate, inorganic	yes	yes	Increase/	adults, mixed	no	n/a	n/a	n/a*	Spr	Fal	33	19,26	61	60,164
	none		none	elderly, female	yes	01 to 07	07 to 13	none[8]*			22		29	
				adults, mixed	yes	23 to 05	11 to 17	not stated*					165	
				adults, male	yes	20 to 02	08 to 14	yes*					24	
PAI-1	yes	yes	none	adults, mixed	yes	03 to 09	13 to 19	yes*	Fal	Spr	166	167	168	169
Plasminogen	none	none	no data	adults, mixed	no	n/a	n/a	n/a	Win	Sum	170	-/-	7	169
Potassium	none	none	none/	adults, male	yes	06 to 12	18 to 24	yes*	n.s.		22,33,47	19,26	20	60
			increase	adults, male	no	n/a	n/a	n/a					24	
Progesterone	yes	yes	no data	elderly, female	yes	03 to 09	15 to 21	yes	Fal-Spr	Sum	4	-/-	2	2
				adults, female					cycle	depend.				115
Prolactin	yes	yes	increase	elderly, male	yes	22 to 04	10 to 16	yes*	n.s.		1,88	171	2	2

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Annual seasonal variations[7] (d) Max	References (a)	References (b)	References (c)	References (d)
				elderly, female	yes	23 to 05	11 to 17	yes*					2	
				adults, male	yes	00 to 06	12 to 18	yes*					24	
PSA, total	yes	yes	none	elderly, male	yes	14 to 20	02 to 08	none	n.s.		172	173	174	175
Prothrombin time (Quick)	yes	yes	decrease	adults, mixed	yes	13 to 19	01 to 07	yes	n.s.		13	14	7	176
				adults, mixed	no	n/a	n/a	n/a					16	
Protein, total	none	none	increase	adults, male	no	n/a	n/a	n/a	n.s.		33	19	24	21
Renin plasma activity	yes	none	increase	adults, mixed	yes	02 to 08	14 to 20	yes*	n.s.		90,177	30	32	178
				adults, male	yes	14 to 20	02 to 08	yes					24	
Reticulocytes	none	yes	increase	adults, male	no	n/a	n/a	n/a	n.s.		95	142	97	179
	yes			adults, male							180			
SHBG	yes	yes	increase	elderly, male	yes	13 to 19	01 to 07	yes	n.s.		27,181	182	27	183
				adults, male	yes	12 to 18	24 to 06	yes	Spr	Win			27	115
Sodium	none	none	none	adults, male	yes	10 to 16	22 to 04	yes	n.s.		22,47	19,26	20	60
				elderly, male	no	n/a	n/a	n/a					24	
Testosterone, total	yes	yes	increase	elderly, female	yes	05 to 11	17 to 23	yes	n.s.		4, 22	182	2	115,184
				adults, male	yes	10 to 16	22 to 04	yes	Spr	Sum			2	2
				elderly, male	yes	05 to 11	17 to 23	yes*	Win	Sum			27	183
				adults, male	yes	05 to 11	17 to 23	yes*					27	
Testosterone, bioavailable	yes	yes	increase	elderly, male	yes	04 to 10	16 to 22	yes*	no data		185	182	27	-/-
				adults, male	yes	04 to 10	16 to 22	yes*					27	
Testosterone, free	yes	yes	no data	elderly, male	yes	04 to 10	16 to 22	yes*	Win	Sum	185	-/-	27	186
				adults, male	no	04 to 10	16 to 22	yes*					27	
Thrombocytes	yes	yes	increase	adults, mixed	yes	17 to 23	05 to 11	yes	Fal	Win	95	96	24	99
				adults, male	yes	12 to 18	24 to 06	yes	Sum	Win			93	104
					no	n/a	n/a	n/a					97	
Thrombocyte function				adults, mixed										
-GP IIb/IIIa expression	no data	no data	none	adults, mixed	yes	06 to 12	18 to 24	yes	no data			167	93	-/-
-P-selectin expression	no data	no data	none	adults, mixed	yes	06 to 12	18 to 24	yes	no data			167	93	-/-

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Annual seasonal variations[7] (d) Max	References (a)	References (b)	References (c)	References (d)
-GP Ib expression	no data	no data	none	adults, mixed	yes	05 to 11	17 to 23	yes	no data			167	93	-/-
-Aggregability (ADP induced)	yes	yes	increase	adults, mixed	yes	17 to 23	05 to 11	yes	Sum	Win	176,187	110,167	93,188	189
-ATP release	no data	no data	no data	elderly, mixed	yes	12 to 18	24 to 06	yes	no data			-/-	93	-/-
Platelet factor 4 (PF4)			increase	elderly, male	yes	12 to 18	24 to 06	yes*	no data			190	190,191	-/-
Thyroxine (T4)	yes	yes	increase	elderly, female	yes	09 to 15	21 to 03	yes	Sum	Spr	22,192	193	2	194
				adults, mixed	yes	09 to 15	21 to 03	yes					2	
Thyroxine, free (fT4)	none	none	none	adults, mixed	no	n/a	n/a	n/a	n.s.		195	193	196	75,195
Tissue plasminogen activator	yes	yes	increase	elderly, male	yes	09 to 11	18 to 21	yes*	Sum	Win	166	167	59	59
						08 to 09								
TNF-α	yes	yes	no data	adults, male	yes	13 to 14	01 to 02	yes[8]	Sum	Win	131	-/-	197	133
Transferrin	none	none	no data	adults, male	yes	12 to 18	24 to 06	yes	Spr-Sum	Fal-Win	1	-/-	97,198	108
Triglycerides	yes	yes	increase	adults, male	yes	15 to 21	03 to 09	yes*	Spr	Fal	22,68,69	19, 71	55	73
				adults, male	yes	19 to 01	07 to 13	yes*					24	
				adults, male	yes	18 to 24	06 to 12	yes*					24	
Triiodothyronine (T3)	none	yes	increase	elderly, male	yes	10 to 16	22 to 04	yes	Sum	Spr	199	193	2	194
				elderly, female	no	n/a	n/a	n/a					2	
				adults, male	yes	05 to 11	17 to 23	none					24	
Triiodothyronine, free (fT3)	none	yes	increase	adults, mixed	yes	01 to 07	13 to 19	yes	n.s.		199	200	196	75
Troponin T	yes	yes	none	elderly, mixed	yes	06 to 10	18 to 22	yes*	no data		201,202	203	204,205	-/-
Troponin I	yes	yes	none	elderly, mixed	no	n/a	n/a	n/a	no data		206	207	204	-/-
TSH	yes	yes	none	elderly, male	yes	23 to 05	11 to 17	yes*	Sum	Win	195	208	2	195
		none		elderly, female	yes	23 to 05	11 to 17	yes*			22		2	
				adults, mixed	yes	00 to 06	12 to 18	yes*					196	
				adults, male	yes	23 to 05	11 to 17	yes*					24	
Type I collagen C-telopeptide	yes	yes	decrease	elderly, male	yes	00 to 06	12 to 18	yes*	Win	Spr	52	156	160	209
(β-CTX)				adults, female	yes	00 to 06	12 to 18	yes*	n.s.				160	158
				elderly, female	yes	00 to 06	12 to 18	yes*					160	

Analyte	Gender[a](1)	Age[a](1)	Posture (b) as compared to supine position[2]	Diurnal variations (c) Population[3] [Age, Gender]	Diurnal Rhythm[4]	Clock hours[5] Peak	Clock hours[5] Trough	Clinical Relevance[6]	Annual seasonal variations[7] (d) Min	Annual seasonal variations[7] (d) Max	References (a)	References (b)	References (c)	References (d)
Urea nitrogen	yes	yes	decrease/	adults, male	yes	18 to 00	06 to 12	none	Fal	Spr	22,33	19, 26	20	60
			none	adults, male	yes	20 to 02	08 to 14	yes*					24	
Uric acid	yes	yes	none	adults, male	yes	02 to 08	14 to 20	None	Fal-Win	Sum	22,33	19,26	20	60
				adults, male	yes	22 to 04	10 to 16	Yes					24	
β-carotene (pro-vitamin A)	yes	yes	no data	adults, male	yes	22 to 04	10 to 16	none[8]	Win	Spr-Sum	210	-/-	211	212
Vitamin B12 (Cobalamin)	none	none	no data	adults, male	no	n/a	n/a	n/a	n.s.		22,107	-/-	97	112
Vitamin C (ascorbic acid)	yes	none	no data	adults, mixed	yes	16 to 22	04 to 10	none[8] *	Win	Sum	149	-/-	213	103
				adults, mixed	yes	12 to 18	24 to 06	none[8] *					213	
				adults, mixed	yes	13 to 19	01 to 07	none[8] *					213	
				elderly, mixed	yes	07 to 13	19 to 01	none[8] *					213	
				adults, male	yes	23 to 5	11 to 17	none[8]					211	
Vitamin D, 25-OH	none	none	no data	elderly, mixed	yes	08 to 14	20 to 02	yes*	Win-Spr	Sum-Fal	107	-/-	61	214,52,65
Vitamin D, 1,25-OH_2	yes	yes	no data	elderly, female	yes	13 to 19	01 to 07	yes	Sum	Win	215	-/-	29	214
Vitamin D-binding protein	yes	yes	no data	elderly, female	yes	17 to 23	01 to 07	yes	n.s.		216	-/-	29	217,218
Vitamin E (α-tocopherol)	none	yes	no data	adults, male	yes	22 to 04	10 to 16	none[8]	Win	Spr-Sum	210	-/-	211	103,212
VWF antigen (vWF:Ag)	none	yes	none	adults, male	yes	09 to 15	21 to 03	yes*	Win	Sum	219	167	105	59
VWF activity (vWF:Rco)	none	yes	no data	adults, male	no	n/a	n/a	n/a*	no data		219	-/-	105	-/-

Supplemental table 3

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
17-β-estradiol	elderly, female	pg/mL	8.40	16%	1.360	1.710°
17-hydroxy-progesterone	elderly, male	ng/mL	1.07	49%	0.520	0.228°*
	elderly, female	ng/mL	0.38	121%	0.460	0.149°*
α-1-antitrypsin	adults, mixed	mg/dl	no data	no data	no data	n/a°
α-2-macroglobulin	adults, mixed	no data	no data	no data	no data	n/a
ACTH	elderly, male	pg/mL	29.6	68%	20.20	7.141°*
	elderly, female	pg/mL	10.3	101%	10.40	3.305°*
aPTT	adults, mixed	sec	no data	no data	no data	n/a°
				intentionally empty row		
ALAT	adults, male	U/L	22.1	3.7%	0.820	4.119
	adults, mixed	µkat/L	no data	6.1%	no data	n/a
	adults, male	U/L	37.4	3.4%	1.272	6.381
Albumin	adults, mixed	g/L	42.4	8.2%	3.480	3.620°
	elderly, female	µmol/L	600	12%	68.00	52.09*
	adults, male	g/L	45.0	3.1%	1.400	3.723
Aldosterone	elderly, male	ng/dl	5.40	83%	4.460	1.235°*
	elderly, female	ng/dl	7.30	72%	5.280	1.544°*
	adults, mixed	ng/dl	6.23	42%	2.600	1.222°*
Alkaline	adults, mixed	µkat/L	no data	2.9%	no data	n/a
phosphatase (AP)	adults, male	U/L	76.9	2.4%	1.846	10.40
Amylase, pancreatic	adults, male	U/L	24.9	5.9%	1.480	4.506
	adults, mixed	µkat/L	no data	1.1%	no data	n/a
ANP $_{(99-126)}$	adults, male	pg/ml	76.1	52%	39.72	17.01°*
				intentionally empty row		
pro-ANP $_{(1-30)}$	adults, male	pg/ml	2149	67%	1444	451.6°*
31 - 67 pro-ANP $_{(31-67)}$	adults, male	pg/ml	2021	69%	1399	716.1°*
Antithrombin	adults, mixed	%	no data	no data	no data	n/a
	elderly, male	%	95.0	15%	14.40	8.064°*
	adults, male	%	83.0	3.4%	2.840	6.411°
ASAT	adults, mixed	µkat/L	no data	4.6%	no data	n/a
	adults, male	U/L	26.2	13%	3.320	3.326
	adults, male	U/L	21.8	4.2%	0.916	2.771
Bilirubin, total	adults, male	µmol/L	7.92	60%	4.720	1.748*
	adults, male	mg/dL	0.77	27%	0.205	0.138°*
Bone-specific AP (BAP)	elderly, female	µg/L	14.9	12%	1.830	2.423°
	elderly, male	µg/L	12.3	11%	1.290	1.883°
C-peptide	elderly, male	ng/mL	3.82	85%	3.260	0.701°*
	elderly, female	ng/mL	3.50	95%	3.320	0.667°*
	adults, male	pmol/L	934	77%	720.0	334.7°*
CRP, high-sensitive	adults, mixed	mg/L	2.59	16%	0.420	0.940
	adults, mixed	mg/L	1.03	34%	0.700	0.470°*
Calcium, total	elderly, female	mg/dL	8.72	4.6%	0.400	0.443
	elderly, male	mg/dL	8.64	4.5%	0.390	0.440
	adults, mixed	mg/dL	8.38	11%	0.960	0.441°*

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
	adults, male	mg/dL	9.50	2.0%	0.190	0.470
Calcium, adjusted total	elderly, female	mmol/L	2.40	3.0%	0.070	0.118
Calcium, ionized	adults, mixed	mg/dL	5.70	4.0%	0.228	0.295
				intentionally empty row		
Chloride	adults, male	mEq/L	104	1.2%	1.243	4.613
Cholinesterase, Pseudo-	adults, mixed	µkat/L	133	3.4%	9.044	18.04
Cholesterol, total	adults, mixed	mg/dL	170	29%	49.60	23.35*
	adults, mixed	mg/dL	170	25%	43.00	23.02*
	adults, mixed	mg/dL	167	20%	32.80	22.21*
	elderly, mixed	mg/dL	166	27%	45.40	22.68*
	adults, male	mmol/L	3.88	9.3%	0.360	0.482°
	adults, male	mg/dL	241	1.0%	2.413	26.40
	adults, male	mg/dL	205	3.4%	6.963	23.28
Cortisol	elderly, male	µg/dL	8.90	95%	8.460	2.104°*
	elderly, female	µg/dL	9.50	83%	7.920	2.280°*
	adults, male	µg/dL	7.68	121%	9.280	1.997°*
	adults, mixed	µg/dL	9.57	38%	7.300	2.178°*
	adults, male	µg/dL	8.50	123%	10.44	2.182°*
Creatine kinase	adults, mixed	µkat/L	no data	6.7%	no data	n/a
	adults, mixed	µkat/L	no data	7.7%	no data	n/a
	adults, male	U/L	132	26%	34.36	26.49*
Creatinine	elderly, female	µmol/L	84.0	15%	12.00	8.421*
	adults, male	mg/dL	1.30	13%	0.169	0.118°*
	adults, male	µmol/L	80.8	3.1%	2.480	7.443
Cystatin C	adults, male	mg/L	0.68	8.8%	0.060	0.089
D-Dimer	adults, mixed	ng/mL	162	no data	no data	n/a
				intentionally empty row		
DHEAS	elderly, male	ng/mL	603	22%	130.0	158.5°
	elderly, female	ng/mL	331	20%	66.00	94.01°
Dopamine	mixed, male	µg/L	3.90	57%	2.240	1.016°*
	mixed, female	µg/L	5.91	65%	3.840	1.560°*
Epinephrine	adults, mixed	pg/mL	25.0	68%	17.00	7.540°*
	adults, male	pg/mL	25.6	52%	13.38	7.290°*
Erythrocytes	adults, male	mill / mm^3	5.11	3.4%	0.174	0.332°
	adults, male	10^{12}/L	4.78	6.3%	0.300	0.318°
MCH	adults, male	pg/ cell	26.8	1.4%	0.375	1.757
MCH	adults, male	fmol	1.85	0.8%	0.014	0.118
MCV	adults, male	fL	84.5	0.6%	0.507	4.946°
	adults, male	fL	86.5	0.1%	0.100	5.030
MCHC	adults, male	g/dL	35.3	2.0%	0.706	1.361°
	adults, male	mmol/L	21.4	0.6%	0.120	0.823
RDW-CV%	adults, male	%	13.9	1.2%	0.167	1.008
	adults, male	%	12.7	0.3%	0.040	0.932
Factor II, activity	adults, mixed	%	no data	no data	no data	n/a
Factor V, activity	adults, mixed	%	no data	no data	no data	n/a
Factor VII, activity	adults, mixed	%	103	5.4%	11.00	12.47
Factorr VII, antigen	adults , male	%	90.0	2.2%	4.000	12.84

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
Factor VIII:C, activity	adults, male	KIU/L	no data	no data	no data	n/a°
	adults, male	KIU/L	no data	no data	no data	n/a
Factor VIII:CAg, antigen	adults, mixed	KIU/L	1.29	22%	0.280	0.204*
Factor IX, activity	adults, mixed	%	no data	no data	no data	n/a
Factor X, activity	adults, mixed	%	no data	no data	no data	n/a
Factor XI, activity	adults, mixed	%	no data	no data	no data	n/a
Factor XII, activity	adults, mixed	%	no data	no data	no data	n/a
Ferritin	adults, male	µg/L	79.7	13%	10.00	20.35
Fibrinogen (Clauss)	adults, mixed	mg/dl	no data	no data	no data	n/a°
				intentionally empty row		
Folate	adults, male	nmol/L	11.4	27%	3.100	2.229°*
FSH	elderly, male	mIU/mL	21.4	6.3%	1.340	3.272°
	elderly, female	mIU/mL	91.5	3.2%	2.920	14.61
				intentionally empty row		
				intentionally empty row		
γ-GT	adults, mixed	µkat/L	no data	5.3%	no data	n/a
	adults, male	U/L	19.9	29%	5.731	4.173*
	adults, male	U/L	18.6	6.5%	1.200	3.672
Gastrin	adults, male	pg/ml	35.1	41%	14.46	10.30°*
Glucose, fasting	adults, male	mg/dL	94.5	21%	20.03	8.318°*
	adults, male	mmol/L	5.08	14%	0.700	0.438°*
HbA1c	adults, male	mmol/mol	33.9	3.4%	1.140	3.709
HDL-C	adults, male	mmol/L	1.36	8.8%	0.120	0.183
	adults, mixed	mg/dL	41.6	61%	25.20	6.548*
	adults, mixed	mg/dL	47.9	55%	26.20	7.233*
	adults, mixed	mg/dL	46.3	59%	27.20	7.122*
	elderly, mixed	mg/dL	38.6	54%	20.80	6.613*
	adults, male	mg/dL	41.1	4.0%	1.644	5.660
Hematocrit	adults, male	%	43.2	3.8%	1.642	2.957
	adults, male	L/L	0.41	4.9%	0.020	0.028°
Hemoglobin	adults, male	mg/dL	15.2	2.4%	0.365	0.831
	adults, male	mmol/L	8.84	6.6%	0.580	0.498°*
Human growth hormone	elderly, male	ng/mL	1.58	37%	0.580	0.550°*
	elderly, female	ng/mL	1.87	31%	0.580	0.576*
Immunoglobulin G	elderly, mixed	mg/dl	1780	13%	240.0	201.1°*
				intentionally empty row		
Immunoglobulin A	elderly, mixed	mg/dl	372	16%	60.00	59.71°*
				intentionally empty row		
Immunoglobulin M	elderly, mixed	mg/dl	127	13%	16.00	22.25°
				intentionally empty row		
Insulin	elderly, male	µU/mL	33.6	95%	32.00	8.148°*
	elderly, female	µU/mL	29.3	100%	29.20	7.248°*
	adults, male	µIU/ml	26.9	153%	41.26	7.821°*
Interleukin-6	mixed, mixed	pg/mL	0.70	24%	0.166	0.090°*
				intentionally empty row		
Iron	adults, male	umol/L	14.1	57%	8.000	2.632*
LDH	adults, male	U/L	139	14%	19.50	17.97*

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
	adults, male	U/L	139	12%	16.38	17.85
	adults, mixed	µkat/L	no data	5.0%	no data	n/a
LDL-C	adults, male	mmol/L	2.01	16%	0.320	0.334°
	adults, male	mg/dL	130	10%	13.02	18.56
Leptin	elderly, male	ng/ml	9.47	60%	5.660	1.061°*
Leukocytes	adults, male	10^9/L	6.19	25%	1.560	0.815°*
	adults, male	1000/mm^3	7.45	14%	1.028	0.910*
Basophils, rel.	adults, male	%	1.00	24%	0.240	0.190*
Basophils, abs.	adults, male	10^9/L	0.02	0.0%	0.000	0.004
	adults, male	cells / mm^3	76.0	36%	27.51	15.49°*
Eosinophils, rel.	adults, male	%	no data	no data	no data	n/a
Eosinophils, abs.	adults, male	cells / mm^3	279	36%	100.4	65.89°*
	adults, male	10^9/L	0.16	50%	0.080	0.043°*
Neutrophils, rel.	adults, male	%	56.1	21%	11.78	5.721°*
Neutrophils, abs.	adults, male	cells / mm^3	4218	41%	1729	680.5°*
	adults, male	10^9/L	3.18	19%	0.620	0.497°*
Monocytes, rel.	adults, male	%	6.10	14%	0.830	0.856°
Monocytes, abs.	adults, male	cells / mm^3	449	no data	no data	n/a
	adults, male	10^9/L	0.53	23%	0.120	0.070°*
Lymphocytes, rel.	adults, male	%	32.1	34%	11.04	4.305°*
Lymphocytes, abs.	adults, male	cells / mm^3	2337	25%	584.3	294.8°*
	adults, male	10^9/L	2.29	43%	0.980	0.309°*
Lymphozyte subpopulations						
T-Lymphocytes (CD3+)	adults, male	/µL	1902	41%	775.8	312.2*
CD4+ T-helper celIs		/µL	1120	44%	488.0	194.9*
Naive CD4+ T-helper celIs		µL	510	52%	263.3	114.2*
Central memory CD4+ T-helper celIs		µL	350	43%	149.2	63.93*
Effector memory CD4+ T-helper celIs		µL	221	38%	84.62	39.94*
Terminal Effector CD4+ T-helper celIs		µL	no data	no data	no data	n/a
CD8+ cytotoxic T cells		µL	659	43%	280.0	123.8*
Naive CD8+ cytotoxic T cells		µL	326	59%	192.4	84.97*
Central memory CD8+ cytotoxic T cells		µL	86.5	35%	30.66	20.49*
Effector memory CD8+ cytotoxic T cells		µL	189	26%	49.44	39.43*
Terminal Effector CD8+ cytotoxic T cells		µL	66.7	21%	13.92	23.85
B-Lymphocytes (CD19+)	adults, male	/nL	0.36	50%	0.180	0.125*
Natural-killer cells	adults, male	/nL	0.22	73%	0.160	0.133*
LH	elderly, male	mIU/mL	17.7	3.4%	0.600	2.590
	elderly, female	mIU/mL	57.9	5.1%	2.980	9.866
				intentionally empty row		
				intentionally empty row		
Lipase	adults, mixed	µkat/L	no data	5.7%	no data	n/a
				intentionally empty row		
Lipoprotein (a)	elderly, male	mg/dL	12.3	20%	2.470	5.067°
Magnesium	adults, male	mmol/L	0.81	1.0%	0.008	0.055
	adults, male	mg/dL	1.96	3.0%	0.059	0.134
Melatonin	adults, male	nmol/L	52.6	149%	78.27	10.19°*
	adults, male	ng/L	13.6	291%	39.60	3.542°*
Myoglobin	adults, male	ng/mL	21.0	40%	12.00	4.691°*

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
	adulds, female	ng/mL	16.0	40%	8.000	4.046°*
Norepinephrine	adults, male	pg/mL	239	60%	142.8	49.14°*
Osteocalcin	elderly, female	ng/ mL	8.27	19%	1.590	1.824°
	elderly, male	ng/ mL	9.07	16%	1.490	1.718°
	adults, female	ng/mL	10.2	6.8%	1.380	1.880
Osteoprotegerin	elderly, male	pmol/L	4.08	15%	0.600	0.310°*
	adults, female	pmol/L	3.66	10%	0.380	0.280°*
	elderly, female	pmol/L	4.74	24%	1.140	0.363°*
	adults, female	pmol/L	3.20	2.8%	0.180	0.247
iPTH, 1-84	elderly, female	pg/mL	26.5	28%	7.300	4.207°*
	elderly, male	pg/mL	41.2	27%	11.11	6.212°*
	elderly, male	pmol/L	5.39	16%	0.880	0.763°*
	adults, female	pmol/L	4.73	17%	0.800	0.679°*
	elderly, female	pmol/L	5.83	16%	0.940	0.820°*
	elderly, female	pmol/L	4.10	34%	1.200	0.627°*
Phosphate, inorganic	adults, mixed	mg/dL	4.79	13%	0.640	0.548*
	elderly, female	mmol/L	1.38	24%	0.300	0.140*
	adults, mixed	mmol/L	1.14	30%	0.340	0.146*
	adults, male	mg/dL	3.82	16%	0.611	0.458°*
Plasminogen activator inhibitor-1	adults, mixed	ng/mL	1.60	78%	1.240	1.184°*
Plasminogen	adults, mixed	no data	no data	no data	no data	n/a
Potassium	adults, male	mmol/L	3.88	9.3%	0.360	0.255°*
	adults, male	mEq/L	4.10	3.8%	0.156	0.261
Progesterone	elderly, female	pg/mL	91.0	37%	34.00	54.54°
				intentionally empty row		
Prolactin	elderly, male	ng/mL	21.1	49%	10.40	3.752°*
	elderly, female	ng/mL	22.5	61%	13.80	4.373°*
	adults, male	ng/ml	6.60	59%	3.920	1.439°*
PSA, total	elderly, male	ng/mL	2.75	11%	0.380	1.003
Prothrombin time (Quick)	adults, mixed	sec	no data	no data	no data	n/a°
				intentionally empty row		
Protein, total	adults, male	mg/dL	6.80	1.6%	0.109	0.417
Renin plasma activity	adults, mixed	ng/mL/h	1.15	26%	0.300	0.277*
	adults, male	ng/ mL	1.90	20%	0.384	0.416°
Reticulocytes	adults, male	10^9/L	43.6	10%	4.400	6.129
				intentionally empty row		
SHBG	adults, male	nmol/L	24.2	8.2%	1.980	4.503°
	elderly, male	nmol/L	28.8	10%	2.980	5.123°
Sodium	adults, male	mmol/L	140	1.6%	2.200	3.953°
	adults, male	mEq/L	140	0.4%	0.560	3.936
Testosterone, total	elderly, male	ng/mL	5.14	21%	1.060	0.912°
	elderly, female	ng/mL	0.36	22%	0.080	0.070°
	adults, male	nmol/L	18.1	49%	8.940	3.554°*
	elderly, male	nmol/L	15.7	37%	5.740	3.019°*
Testosterone, bioavailable	adults, male	nmol/L	4.25	44%	1.880	0.951°*
	elderly, male	nmol/L	3.66	27%	1.000	0.781°
Testosterone, free	adults, male	pmol/L	490	51%	248.0	95.61°*
	elderly, male	pmol/L	393	39%	155.0	76.02°*

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
Thrombocytes	adults, male	1000/mm^3	240	5.6%	13.42	31.11°
	adults, mixed	10^5 / µL	2.00	6.0%	0.120	0.271°
	adults, male	10^9/L	223	4.9%	10.84	29.32
Thrombocyte function						
GP IIb/IIIa expression	adults, mixed	% pos. PLT	30.0	17%	5.100	n/a°
P-selectin expression	adults, mixed	MFI	3.67	6.0%	0.220	n/a°
GP Ib expression	adults, mixed	MFI	220	9.0%	19.80	n/a°
Aggregability (COL induced)	adults, mixed	AUC (Ω x min)	82.0	4.0%	3.300	9.605°
ATP release	adults, mixed	nM	0.50	16%	0.080	n/a°
Platelet factor 4 (PF4)	elderly, mixed	(IU/ml)	17.5	154%	27.00	4.744°*
Thyroxine (T4)	elderly, male	µg/dL	7.67	8.6%	0.660	1.010°
	elderly, female	µg/dL	7.31	5.7%	0.420	1.009°
Thyroxine, free (fT4)	adults, mixed	pmol/L	16.2	1.2%	0.194	1.691
Tissue plasminogen activator	adults, mixed	ng/mL	4.50	54%	4.860	1.553°*
TNF-α	elderly, male	pg/mL	no data	22%	no data	n/a°
Transferrin	adults, male	umol/L	30.8	9.1%	2.820	3.325°
Triglycerides	adults, male	mmol/L	1.12	66%	0.740	0.228°*
	adults, male	mg/dL	236	41%	95.73	39.89°*
	adults, male	mg/dL	211	43%	90.98	36.31°*
Triiodothyronine (T3)	elderly, male	ng/dL	93.8	8.0%	7.500	11.81°
	elderly, female	ng/dL	95.3	3.2%	3.060	11.73
	adults, male	%	29.9	1.8%	0.538	4.594
Triiodothyronine, free (fT3)	adults, mixed	pmol/L	5.42	6.9%	0.374	0.581°
Troponin T	elderly, mixed	ng/L	14.2	5.8%	4.100	1.912°*
Troponin I	elderly, mixed	ng/L	no data	n/a	n/a	n/a
TSH	elderly, male	µIU/mL	3.56	29%	1.040	0.733°*
	elderly, female	µIU/mL	4.33	24%	1.060	0.896°*
	adults, mixed	mIU/L	1.78	49%	0.878	0.458°*
	adults, male	µIU/ml	3.70	90%	3.323	0.926°*
Type I collagen C-telopeptide	elderly, male	µg/L	0.21	95%	0.200	0.059°*
(β-CTX)	adults, female	µg/L	0.14	86%	0.120	0.043°*
	elderly, female	µg/L	0.36	89%	0.320	0.102°*
Urea nitrogen	adults, male	mmol/L	5.37	8.2%	0.440	0.685
	adults, male	mg/dL	16.6	18%	2.988	2.568°*
Uric acid	adults, male	mmol/L	0.33	7.9%	0.026	0.038
	adults, male	mg/dL	6.40	4.0%	0.256	0.701°
β-carotene (pro-vitamin A)	adults, male	no data	0.45	8.4%	0.038	0.122
Vitamin B12 (Cobalamin)	adults, male	pmol/L	299	14%	41.64	69.95
Vitamin C (ascorbic acid)	adults, mixed	mg/dL	0.59	44%	0.260	0.044*
	adults, mixed	mg/dL	0.71	48%	0.340	0.051*
	adults, mixed	mg/dL	0.89	72%	0.640	0.074*
	elderly, mixed	mg/dL	0.62	26%	0.160	0.037*
	adults, male	µmol/L	34.9	13%	4.520	6.985
Vitamin D, 25-OH	elderly, mixed	ng/mL	11.5	24%	2.720	2.469°*
Vitamin D, 1,25-OH_2	elderly, female	pmol/L	106	14%	14.00	17.09°
Vitamin D-binding protein (DBP)	elderly, female	µmol/L	4.20	15%	0.600	0.615°
Vitamin E (α-tocopherol)	adults, male	no data	20.9	13%	2.760	3.671

Analyte	Population [age, sex]	Unit	MESOR[1]	Peak to trough amplitude: percentage of MESOR[2]	Peak to trough amplitude: absolute Dxi[2]	pD_2[3]
VWF antigen (vWF:Ag)	adults, male	KIU/L	0.84	45%	0.380	0.141°*
VWF activity (vWF:Rco)	adults, male	KIU/L	1.38	23%	0.320	0.176*

Table 4

Common query term			
((English[Language] OR German[Language])) AND ("1950"[Date - Publication] : "3000"[Date - Publication]) AND (<*measurands_name*> OR <*synonyms*>) AND humans) AND (<<*specific query as stated below*>>[All Fields]); - First line restriction: [All Fields] replaced by [Title/Abstract];			
Common mandatory Inclusion criteria			
Report describes impact of search target on measurand levels in healthy individuals AND age of individuals investigated ≥ 18 years			
Search target	**Specific query terms**	**Major criteria**	**Minor criteria**
Diurnality	(circad* OR diurn*). - Second line restriction: "AND (chronobiol*)" added to specific query	- Results of cosinor analysis or at least analyses of variance provided - Analyte levels fit to independently reported RL of the respective analytical method.	- Twentyfour hours coverage - Appropriate number of time points of blood sampling - Illustration of times courses - Known analytical variation - Age and gender of individuals provided - Comment on clinical relevance
Seasonality	(annual* OR circann* OR season*) - Second line restriction: "AND (chronobiol*)" added to query	- Follow up study - Results of cosinor analysis or at least analyses of variance provided	- Twelve month coverage - Known analytical variation - Age and gender of individuals provided
Posture	(postur* OR sitting OR supin*) - Second line restriction: query term replaced by "(Posture[MeSH Terms]"	- Supine position included - Statistical analysis of changes provided	- Time frames of respective posture fit to clinical blood collection procedure - Age and gender of individuals provided - Known analytical variation
Gender	(gender* OR sex*) AND (depend* OR (reference AND (value* OR limit* OR range* OR interval*))) - Second line restriction: "AND (reference values[MeSH Terms]" added to query.	- Analyte levels fit to independently reported RL of the respective analytical method - Statistical analysis of differences provided	- Stratification included age - Analyte levels fit to results reported for diurnality - Known analytical variation - Caucasian origin of reference individuals
Age	(age* AND [depend* OR (reference AND (value* OR limit* OR range* OR interval*))) - Second line restriction: "AND (reference values[MeSH Terms]" added to query.	- Statistical analysis of age-specific changes provided	- Stratification included gender - Time course of changes provided - Analyte levels fit to results reported for diurnality - Known analytical variation - Caucasian origin of reference individuals