The Dim Light Melatonin Onset (DLMO) across ages, methodologies and sex and its relationship with Morningness/Eveningness.

David J. Kennaway

Robinson Research Institute and Adelaide School of Medicine,

University of Adelaide,

Adelaide Health and Medical Science Building,

North Terrace, Adelaide,

South Australia, Australia.

Corresponding author:

David J. Kennaway

Email: david.kennaway@adelaide.edu.au

https://orcid.org/0000-0002-5864-3514

Supplementary File 1

The papers reporting Saliva DMLO used in the current study

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Supplementary File 2

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Supplementary File 3.

The source and type of data obtained in the data sets made available by researchers or mined from the literature.

Reference	Individual provider of the data and their institution	Source	DLMO	Age	MEQ
[1]	Stephanie J. Crowley, Rush University Medical Center, USA	Data Share	Y	Y	Y
[2-4]	Erlend Sunde, University of Bergen, Norway,	Data Share	Y	Y	Y
[5]	Thomas Kantermann, University of Applied Science, Essen, Germany	Data Share	Y	Y	Y
[6]	J. Matthew Thomas, University of Kentucky, USA	Data Share	Y	Y	Y
[7]	Andrew Reiter, Central Queensland University, Adelaide, Australia	Data Share	Y	Y	Y
[8]	Ranjay Chakraborty, Flinders University, Australia	Data Share	Y	Y	Y
[9]	Mary Carskadon, Brown University, USA	Data Share	Y	Y	Y
[10]	Emily J. Ricketts, University of California Los Angeles, USA	Data Share	Y	Y	Y
[11]	Takafumi Fukuda, Kirin Company, Ltd., Japan;	Data Share	Y	Y	Y
[12]	Christophe Moderie, McGill University, Canada	Data Share	Y	Y	Y
[13]	Sarah C. Flanagan, Ulster University, Northern Ireland	Data Share	Y	Y	Y
[14]	Nicole Lovato, Flinders University Australia	Data Share	Y	Y	Y
[15]	Raffaele Manni, IRCCS Mondino Foundation, Pavia, Italy.	Data Share	Y	Y	Y
[16, 17]	Elise M McGlashan, Monash University, Australia	Data Share	Y	Y	Y
[18]	Madison K Titone, University of California, San Diego. USA	Data Share	Y	Y	Y
[19]	Meredith Coles, Binghamton University, NY, USA	Data Share	Y	Y	Y
[20]	Kathryn Reid, Northwestern University, USA	Data Share	Y	Y	Y
[21]	Shigekazu Higuchi, Kyushu University, Japan	Data Share	Y	Y	Y
[22]	Gorica Micic, Flinders University, Australia	Data Share	Y	Y	Y
[23, 24]	Tracey Sletten, Monash University, Australia	Data Share	Y	Y	Y

[25]	Camilla Hoyos, University of Sydney, Australia	Data Share	Y	Y	Y
[26]	Kelly Baron, University of Utah, USA	Data Share	Y	Y	Y
[27]	Giulia Zerbini, University of Augsburg, Germany.	Data Share	Y	Y	N
[28]	Eun Yeon Joo, Sungkyunkwan University School of Medicine, Korea	Data Share	Y	Y	N
[29]	Carolin Reichert, University of Basel, Switzerland	Data Share	Y	Y	N
[30]	Beatrix Feigl, Queensland University of Technology, Australia	Data Share	Y	Y	N
[31]	Maria Angeles Rol, University of Murcia, Spain.	Data Share	Y	Y	N
[32]	Stephanie J. Crowley, Rush University Medical Center, USA	Data Share	Y	Y	N
[33]	Monique K. LeBourgeois, University of Colorado Boulder, USA;	Data Share	Y	Y	N
[34]	Aleksandra Domagalik-Pittner, Jagiellonian University, Poland	Data Share	Y	Y	N
[35, 36]	Francis Lévi, Warwick University, United Kingdom	Data Share	Y	Y	N
[37, 38]	Julia Stone, Monash University, Australia	Data Share	Y	Y	N
[39]	Beth Malow, Vanderbilt University School of Medicine, USA	Data Share	Y	Y	N
[40]	Shantha Rajaratnam, Monash University, Australia	Data Share	Y	Y	N
[41]	University of Colorado at Boulder, USA	Paper	Y	Y	N
[42, 43]	Monash University, Australia	Paper	Y	Y	N
[44]	CEMAF, France	Paper	Y	Y	N
[45]	University of South Australia, Australia	Paper	Y	Y	N
[46]	Hôpital du Sacré-Coeur de Montréal, Canada	Paper	Y	Y	N
[47]	Charité Universitätsmedizin Berlin, Germany	Paper	Y	Y	N
[48-50]	Rush University Medical Center, USA	Paper	Y	N	Y
[51]	University of Dortmund, Germany.	Paper	Y	N	Y
[52]	National Institute of Mental Health, Japan,	Paper	Y	N	Y
[53]	University of São Paulo School of Medicine, Brazil	Paper	Y	N	Y

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Supplementary File 4.

The data are the published saliva and plasma DLMO (mean ± SD) from studies which compared younger and older healthy subjects.
Note that in all but 1 study (highlighted) the DLMO of older subjects was earlier than for the younger subjects.

	Saliva/ Plasma	Age	Younger	n	Age	Older	n
[1]	S	26	20.17h	10	69	19.95h	10
[2]	S	30	22.85h ± 1.53	16	50	21.53h ± 1.30	21
[3]	S	25	22.80h ± 1.02	26	65	22.17h ± 0.58	12
[4]	P	27	20.50h ± 0.80	12	70	20.20h ± 0.90	11
[5]	P	23	22.30h ± 1.21	27	69	21.00h ± 1.19	42
[6]	P	23	21.07h ± 0.72	11	66	21.60h ± 1.23	15
[7]	P	21	22.07h ± 1.26	10	71	21.92h ± 0.83	10
[8]	P	23	23.13h ± 1.47	33	68	21.92h ± 1.15	15
[9]	P	27	21.30h ± 1.27	8	58	19.28h ± 1.3	5
[10]	P	29	22.74h ± 1.42	16	67	22.19h ± 1.33	14
[11]	P	27	21.83h ± 1.23	8	64	20.63h ± 0.97	10

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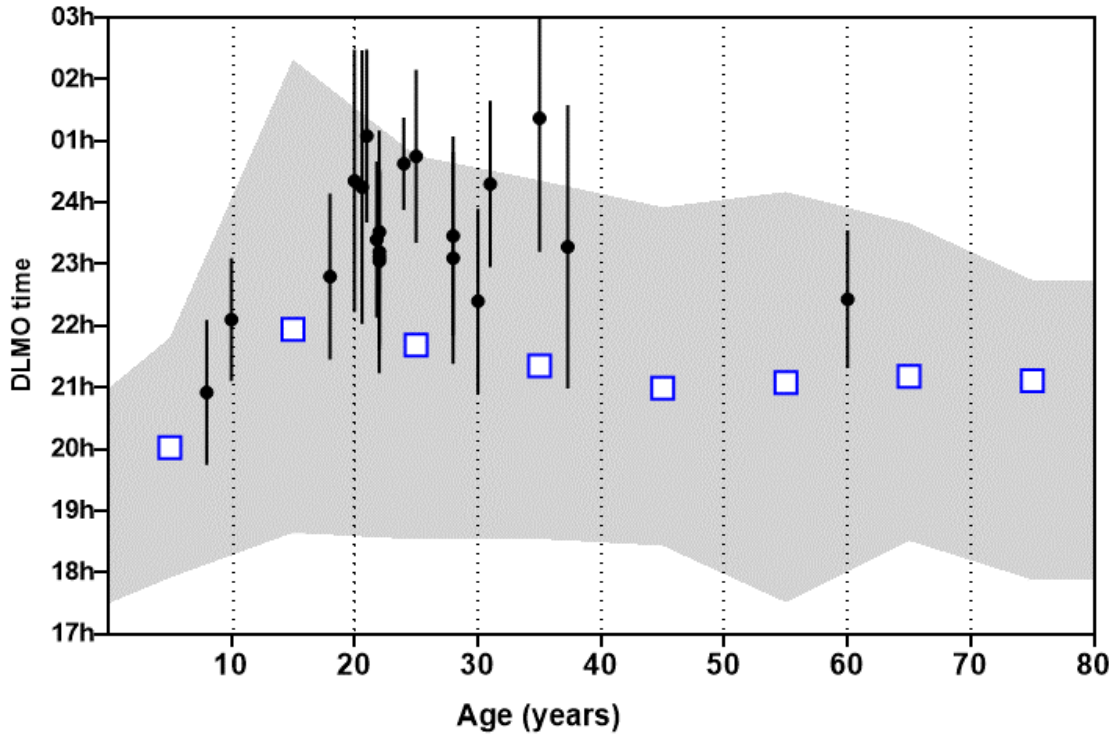
Supplementary File 5

The saliva DLMO (mean ± SD) for subjects clinically diagnosed with DSWPD or similar and their mean ages. Also plotted are the n-weighted saliva DLMO for healthy subjects (□). The reference range for healthy individuals is shown as the shaded area.



The papers used to create the figure above and a brief description of the criteria used for the diagnosis of DSWPD.

Reference	Criteria for diagnosis of DSPS
[1]	Patients met the ICSD-3 criteria A–E for DSWPD.
[2]	Participants reported at least a 2-hour difference between desired and habitual bedtime, subjective sleep latency at the desired bedtime that suggested sleep onset did not occur until the habitual bedtime.
[3]	Subjects had a habitual bedtime later than midnight with a complaint of a difficulty adapting their sleep timing to standard work/school schedules.
[4]	Habitual Bedtime varied from 00:30 to 04:00 hours (01:36 ± 1:14 hours).
[5]	Diagnostic criteria of the ICSD ; (1) problems falling asleep in the evening, (2) falling asleep after 2 am at least three days a week, (3) ability to sleep until early afternoon, (4) problems waking up in time for school/ studies, (5) early wake-up times associated with extreme daytime sleepiness.
[6]	Had evening-type MEQ, a minimum of 2-h discrepancy between their preferred and current sleep pattern, sleep onset later than 1:00 am but sound sleep quality

[7]	DSWPD patients were eligible if their DLMO time was later than 23.00 h and classified as having ‘circadian DSWPD’ with DLMO within 30 min before desired bedtime or after desired bedtime.
[8]	Met the ICSD diagnostic criteria for DSPS including complaints of sleep onset insomnia and phase delay of the major sleep episode using two-week sleep diaries. All had subjective complaints of an inability to initiate sleep at a desired clock time which was earlier than their markedly delayed habitual sleep times.
[9]	Met the ICSD criteria for DSWPD as determined by a sleep physician. Controls had a sleep onset no later than 12:30 am, an intermediate MEQ score (42–58).
[10]	Participants met diagnostic criteria for DSPD based on clinical interview by a sleep physician. Participants were classified into phenotype groups based on the relationship between DLMO and desired bedtime (DBT). A circadian DSPD phenotype was defined as having a DLMO time at or after DBT.
[11]	Idiopathic chronic SOI, defined as a sleep onset later than 20:30 hours for children at age 6 years, and for older children 15 min later per year.
[12]	Subjects met ICSD criteria for DSPS. Reported a delay in sleep and wake times relative to the demands of society and an inability to fall asleep at conventional or desired times, as well as difficulty awakening in the morning.
[13]	DSPD subjects had (a) sleep onset later than 01:00 a.m. (b) late sleep offset and great difficulties rising in the morning; (c) if allowed to choose their own sleep-wake rhythm, they exhibited improved sleep quality and duration for age.
[14]	Presence of a misalignment between the participant’s usual sleep–wake times and routine schedule, prospectively defined as an obligatory morning commitment requiring waking 1–2.5 h earlier than average wake time at least 1 day per week.
[15]	Diagnostic criteria of the ICSD ; (1) problems falling asleep in the evening, (2) falling asleep after 2 am at least three days a week, (3) ability to sleep until early afternoon, (4) problems waking up in time for school/ studies, (5) early wake-up times associated with extreme daytime sleepiness.
[16]	Idiopathic chronic SOI, defined as a sleep onset later than 20:30 hours for children at age 6 years, and for older children 15 min later per year.
[17]	Diagnosis of DSPD according to the standard criteria of the International Classification of Sleep Disorders, second edition (ICSD-2 and a clinical interview conducted by a psychiatrist-sleep specialist.
[18]	Diagnosed with DSWPD according to the ICSD criteria
[19]	Patients met ICSD criteria
[20]	Patients completed an online questionnaire assessing the time of falling asleep, trouble waking up in the morning, sleep maintenance problems, restless legs, snoring, apnoea and daytime sleepiness. Patients falling asleep late or having trouble waking up at a conventional time in the morning were studied.

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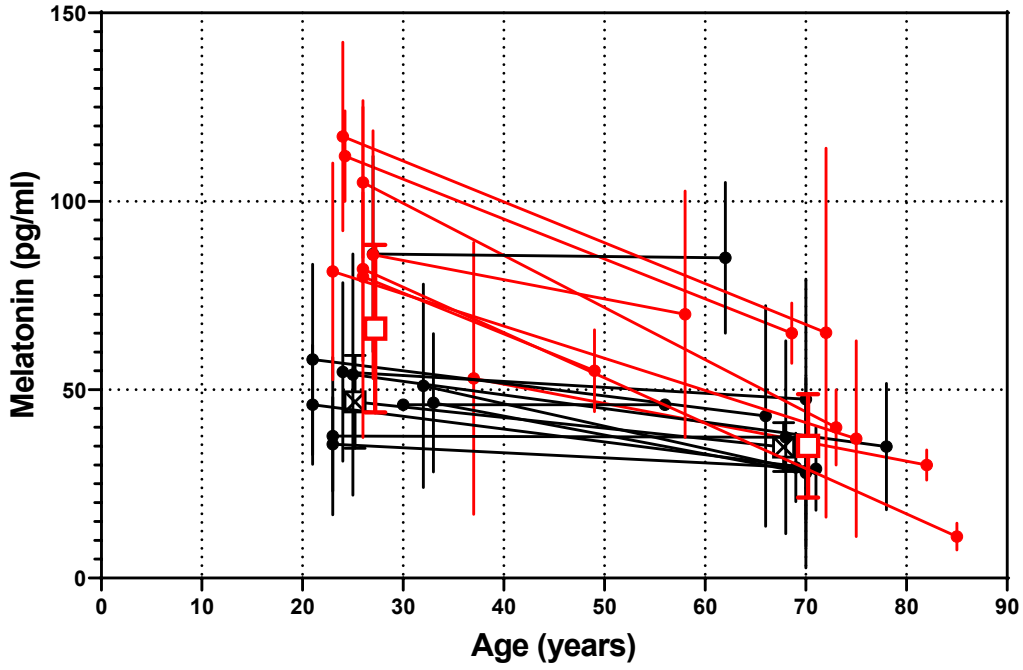
Supplementary File 6.

The peak plasma melatonin levels in healthy subjects at different ages from 18 papers, where both young and older subjects were studied simultaneously. The median rate of change in melatonin levels was determined and studies divided into those changing at rates above (red lines) and below the median (black lines). Note that the weighted mean levels of the "young" fast declining group was higher than the slowly declining group, but means were similar in the older groups.



The following table shows the calculated rate of change in melatonin concentration across the ages. The median was 0.51 pg/ml/yr.

Ref	Change (pg/ml/y)	Ref	Change (pg/ml/y)
[1]	0.00	[2]	0.51
[3]	0.01	[4]	0.51
[5]	0.03	[6]	0.59
[7]	0.13	[8]	0.85
[9]	0.16	[10]	1.06
[11]	0.33	[12]	1.09
[13]	0.34	[14]	1.09
[15]	0.36	[16]	1.20
[17]	0.50	[18]	1.38

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Supplementary File 7.

Correlation of MEQ versus DLMO from individual data sets or mined from the literature.

Ref	Slope	R squared	P value	Deviation from zero?	n	Mean age (y)
[1]	-3.755	0.333	<0.0001	Significant	52	24
[2]	-4.365	0.481	<0.0001	Significant	59	30.5
[3]	-4.097	0.318	<0.0001	Significant	80	22
[4]	-4.525	0.325	<0.0001	Significant	98	26.8
[5]	-3.516	0.507	0.001	Significant	19	31.7
[6, 7]	-3.010	0.343	0.001	Significant	31	22.5
[8]	-2.803	0.232	<0.001	Significant	397	18.8
[9]	-2.103	0.232	0.006	Significant	31	22
[10]	-3.617	0.232	0.013	Significant	26	20
[11]	-1.475	0.075	0.025	Significant	67	21.9
[12]	-2.901	0.376	0.026	Significant	13	22.1
[13]	-4.162	0.199	0.026	Significant	25	21.4
[14]	-1.576	0.086	0.026	Significant	58	27.9
[15]	-3.036	0.329	0.032	Significant	14	23.9
[16]	-1.900	0.063	0.035	Significant	71	23.1
[17, 18]	-3.200	0.258	0.053	Not Significant	15	21.2
[19]	-1.682	0.058	0.080	Not Significant	54	36.4
[20]	2.688	0.258	0.092	Not Significant	12	33.6
[21]	-3.211	0.134	0.103	Not Significant	21	39.9
[22]	-1.998	0.098	0.112	Not Significant	27	23.3
[23]	8.508	0.056	0.112	Not Significant	46	21.4
[24]	-0.933	0.061	0.167	Not Significant	33	32.4
[25]	-3.762	0.089	0.322	Not Significant	13	67.5
[26]	1.270	0.031	0.354	Not Significant	30	21.6
[27]	-0.326	0.005	0.735	Not Significant	27	65.7
[28]	-0.311	0.005	0.772	Not Significant	18	23.8
[29]	0.536	0.007	0.803	Not Significant	12	32.3
[30]	-0.119	0.000	0.871	Not Significant	93	13.4
[31]	-0.145	0.000	0.944	Not Significant	15	9.7
Combined	-2.163	0.147	<0.0001	Significant	1457	

n = the number of data points in the individual studies

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Supplementary File 8

Papers reporting melatonin levels in older normal sleepers and those diagnosed with primary insomnia.

References 1-10 report no difference, while references 11-13 conclude that insomniacs produce less melatonin. The numbers of citations were collected from the Web of Science in July 2022

Ref	Institution	Conclusions	Year of publication	Citations	Citations /year
[1]	University of South Australia and University of Adelaide, Australia.	"No significant differences in melatonin excretion were observed between controls and insomniacs."	1998	24	1
[2]	Department of Psychiatry, University of California, San Diego.	"Total daily excretion of 6-SMT was not significantly related to total sleep time, wake-within-sleep or sleep complaints."	1998	37	1.54
[3]	Department of Psychiatry, University of California, San Diego.	"Data indicate that low melatonin production may not be an important factor in insomnia among the elderly."	1998	33	1.38
[4]	University of South Australia and University of Adelaide, Australia.	"Although insomniacs showed a greater amount of wakefulness, less sleep in total, and lower sleep efficiency, no significant group differences were observed in any of the melatonin parameters."	1999	23	1
[5]	Clinics Hospital, Montevideo, Uruguay and University of Buenos Aires, Argentina	"No strict correlation was found between prior 6-sulphatoxymelatonin levels in urine and subsequent sleep improvement after receiving melatonin."	2000	45	1.96
[6]	Sanatorios Los Arroyos e IPAM, Laboratorio de Analisis Bioquımicos e Inmunologicos, Rosario, Argentina; and University of Buenos Aires, Argentina	"The urinary excretion of aMT6s before starting administration of melatonin correlated negatively and significantly with age, but not with the intensity of the sleep disorder or the outcome of treatment,"	2001	53	2.52

[7]	Waitemata Health Ltd, Auckland, New Zealand, University of Auckland, New Zealand and University of Surrey, UK	"No difference in mean aMT6s 24 hour or total night excretory levels, or night/day ratios."	2001	26	1.24
[8]	Waitemata Health Ltd, Auckland, New Zealand, University of Auckland, New Zealand and University of Surrey, UK	"There was a significant difference between the groups in self-reported sleep quality indicators at entry, but no difference in melatonin secretion."	2003	44	2.32
[9]	Department of Psychiatry and Psychotherapy, Charite–Universitatsmedizin, Berlin, Germany	"Data failed to show any age-controlled partial correlation between 6-sulphatoxymelatonin (aMT6s) parameters and PSG parameters in either of the two groups."	2007	9	0.6
[10]	CPS Research, UK., University of Glasgow, UK. Neurim Pharmaceuticals Ltd. Israel, Tel-Aviv, University, Israel.	"A low melatonin excretion level, regardless of age, is not useful in predicting response to Prolonged Release Melatonin in insomnia".	2010	82	6.83
[11]	Technion Israel Institute of Technology, Israel, Neurim Pharmaceuticals Ltd, Israel, Tel Aviv University and Maccabi Pharmaceuticals Ltd, Israel	"Melatonin deficiency seems to be a key variable in the incidence of sleep disorders in elderly people, and melatonin replacement therapy may prove beneficial."	1994	242	8.64
[12]	Wolfson Medical Center, Bat-Yam, Israel, Neurim Pharmaceuticals Ltd, Maccabi Medical Care and Health Fund, and Tel-Aviv University.	"Peak excretion of the main melatonin metabolite 6-sulphatoxymelatonin during the night was lower than normal and/or delayed in comparison with non-insomniac elderly people."	1995	373	13.81

[13]	Centre du Sommeil, Hotel-Dieu de Paris, Paris, France; Neurim Pharmaceuticals Ltd., Israel; and Tel Aviv University, Israel.	Low nocturnal melatonin production is associated with insomnia in patients aged 55 years or older and identifies patients who are somewhat more likely to respond to melatonin replacement. Melatonin replacement therapy may improve sleep quality by treating an underlying deficiency in the endogenous production of this sleep-regulating hormone.	2004	117	6.5

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